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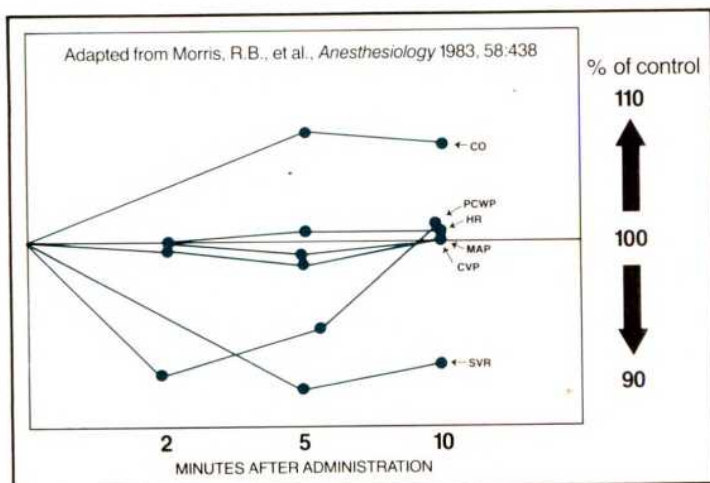
# Anesthesia and Analgesia

Journal of the International Anesthesia Research Society  
Oldest Publication in the Specialty—Established 1922



In neuromuscular blockade...

# Closest to the ideal:



## Free of clinically significant cardiovascular effects

NORCURON is the only surgical muscle relaxant for which no clinically significant adverse cardiovascular effects have been observed in clinical trials.<sup>1,3</sup> This makes NORCURON unique among all neuromuscular blocking agents in clinical use.<sup>4</sup>

The Effect of Non-depolarizing Muscle Relaxants on Histamine Levels, Mean Arterial Pressure and Heart Rate<sup>5</sup>

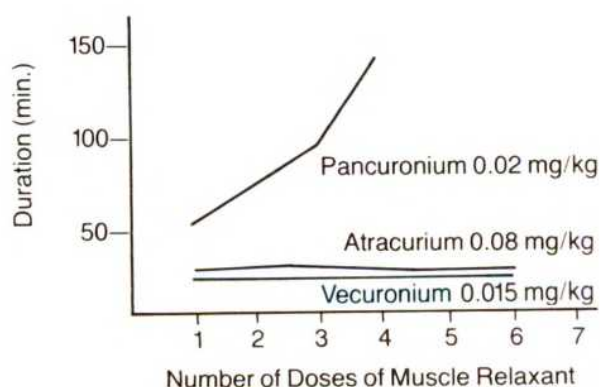
Drug	Dose (mg/kg)	xED <sub>95</sub>	Percent of Control		
			Histamine	Mean Arterial Pressure	Heart Rate
tubocurarine	0.5	1	318	78	116
metocurine	0.5	2	212	79	119
atracurium	0.6	3	192	80	108
vecuronium	0.1	1.7	117	100	99
vecuronium	0.2	3.5	87	99	102

## Histamine release unlikely to occur

Histamine release has not been observed with NORCURON...as shown by preliminary clinical experience. In doses up to 3.5 times the ED<sub>95</sub>, it causes no increase in circulating histamine nor does it decrease systemic blood pressure.<sup>5</sup>

Hypotension and tachycardia tend to occur when histamine levels are increased to about 200% of control.<sup>5</sup>

The Neuromuscular Effects of Maintenance Doses of Vecuronium, Atracurium and Pancuronium<sup>6,7</sup>



## No clinically significant cumulative effects seen

With NORCURON cumulative effects are not seen in clinical practice. The interval between repeated doses has been found to remain constant between as many as six to ten repeated administrations.<sup>6,7</sup>



P24581

# NORCURON<sup>®</sup>

(vecuronium bromide for injection)

CVE - H04006 - 11 - P024581

## Safety Index and Comparative Safety Ratios<sup>8</sup>

$$\text{Safety Index} = \frac{\text{ED}_{50} \text{ autonomic inhibition}}{\text{ED}_{95} \text{ neuromuscular blockade}}$$

### Comparative Safety Ratios

For Vagolytic Effects		For CV/Histamine Related Effects	
gallamine	1:1	d-tubocurarine	1:1
pancuronium	3:1	metocurine	2:1
atracurium	25-30:1	atracurium	3:1
vecuronium	60:1	vecuronium	*

\*cannot be calculated since it does not cause any CV or histamine related effects

## Outstanding safety profile

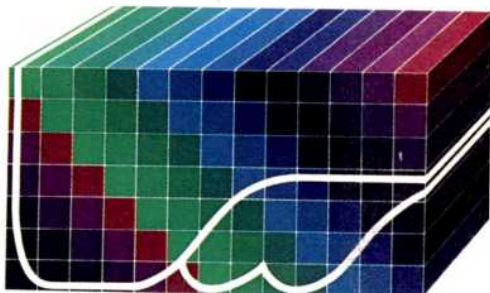
The Safety Index helps quantify the improved safety of the newer muscle relaxants on a relative basis. The characteristics of cardiovascular effects and histamine release are areas where the new agents, particularly NORCURON, have made the most significant gains.<sup>8</sup>

The Safety Index is described as the  $\text{ED}_{50}$  for autonomic inhibition over the  $\text{ED}_{95}$  for neuromuscular blockade.<sup>8</sup>

## A Comparison of Surgical Muscle Relaxants vs. The Ideal<sup>4</sup> (" + " signifies proximity to the ideal)

Characteristic	Vecuronium	Atracurium	Pancuronium	Succinylcholine	D-tubocurarine
Onset of Action	-	-	-	+	-
Histamine Release	+	-	+	+	-
Cardiovascular Side Effects	+	+/-	-	-	-
Duration of Action	+	+	-	+	-
Cumulative Effects	+	+	-	-	-
Rate of Recovery	+	+	-	+	-
Reversibility	+	+	+	-	+
Potency	+	+	+	-	-
Non-depolarizing	+	+	+	-	+
Metabolite Activity	+	+	+	+	+

\*Currently under evaluation.



**NORCURON<sup>®</sup>**  
(vecuronium bromide for injection)

## Closest to the ideal

Of the newer short- to intermediate-acting drugs, NORCURON has the most ideal profile, specifically attributable to its outstanding safety features relating to cardiovascular side effects and histamine-releasing properties.<sup>4</sup>



## References

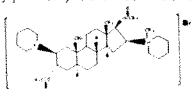
1. Durant RN. Norcuron® — A new non-depolarizing neuromuscular blocking agent. *Semin Anesth* 1:47-56, 1982. 2. Morris RB, Cahalan MK, Miller RD, et al: Cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 58:438-440, 1983. 3. Krieg N, Crul JF, Booy LH: Relative potency of ORG NC45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anesth* 52:783-787, 1980. 4. Miller RD (ed): *Innovations in Surgical Muscle Relaxants*. Far Hills, NJ, Gardiner-Caldwell Synermed, 1984. 5. Basta SA, Savarese JJ: Comparative histamine-releasing properties of vecuronium, atracurium, tubocurarine and metocurine, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC45, vecuronium bromide)*. Amsterdam, Excerpta Medica, 1983. p. 183. 6. Foldes FF, et al: Muscular relaxation with atracurium, vecuronium and Duodur under balanced anaesthesia. *Br J Anaesth* 55 (suppl. 1): 97S, 1983. 7. Fahey MR, Morris RB, Miller RD, et al: Clinical pharmacology of ORG NC45 (Norcuron®): a new non-depolarizing muscle relaxant. *Anesthesiology* 55:6, 1981. 8. Clinical Courier, Vol. 2, No. 4, July 1984.

## NORCURON® (NC-45)

Vecuronium Bromide for Injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

**DESCRIPTION:** NORCURON® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-(2-p, 3v, 5a, 16β, 17β)-3, 17-bis (acetoxyl)-2-(1'-piperidinyl)androstan-16-yl-1-methyl-, bromide. The structural formula is:



Norcuron® is supplied as a sterile freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

**CLINICAL PHARMACOLOGY:** Norcuron® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1.3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is longer than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED<sub>50</sub> (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® (vecuronium bromide for injection) may be decreased by approximately 15% (see Dosage and Administration Section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to a 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started the neuromuscular block produced by Norcuron® (vecuronium bromide for injection) is readily reversed with various anticholinesterase agents, e.g., pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

**Pharmacokinetics:** At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dose range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/min/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of the injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron® (vecuronium bromide for injection); equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half of the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from the patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary-capillary-wedge-pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiovascular disease.) Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® (vecuronium bromide for injection) has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

**INDICATIONS AND USAGE:** Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** None known.

**WARNINGS:** NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

## PRECAUTIONS:

**Renal Failure:** Norcuron® (vecuronium bromide for injection) is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

**Altered Circulation Time:** Conditions associated with slower circulation time in cardiovascular disease, old age, or edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

**Hepatic Disease:** Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in recovery from Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

**UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.**

**Severe Obesity or Neuromuscular Disease:** Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron® (vecuronium bromide for injection).

**Malignant Hyperthermia:** Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

**Drug Interactions:** Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY).

The use of Norcuron® (vecuronium bromide for injection) before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied. Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

**Inhalational Anesthetics:** Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

**Antibiotics:** Parenteral intraperitoneal administration of high doses of certain antibiotics may intensify or produce a neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium chloramphenicol. If these or other newly introduced antibiotics are used in conjunction with Norcuron® (vecuronium bromide for injection) during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

**Other:** Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

**Drug/Laboratory Test Interactions:** None known.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

**Pregnancy: Pregnancy Category C:** Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

**Pediatric Use:** Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1 1/2 times as long to recover. Information presently available does not permit recommendations for usage in neonates.

**ADVERSE REACTIONS:** Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

**OVERDOSAGE:** There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Norcuron® (vecuronium bromide for injection) can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve. Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

**DOSAGE AND ADMINISTRATION:** Norcuron® (vecuronium bromide for injection) is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain the maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.7 times the ED<sub>50</sub>) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® (vecuronium bromide for injection) is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

**Dosage in children:** Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1 1/2 times as long to recover. See also sub-section of PRECAUTIONS titled Pediatric use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

**COMPATIBILITY:** Norcuron® is compatible in solution with 0.9% NaCl solution 5% glucose in water 5% glucose in saline Lactated Ringers

**HOW SUPPLIED:** 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 12. NDC 0052-0442-10

**STORAGE:** PROTECT FROM LIGHT Store at 15°-30°C (59°-86°F)

**AFTER RECONSTITUTION:** Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F) DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.

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**ORGANON PHARMACEUTICALS,** a Division of

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# Anesthesia and Analgesia

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# THROUGHOUT THE PERI

to relieve excessive anxiety

## Rapid relief of anxiety and apprehension

Anxiety is an extremely common reaction to the stress of anesthesia and surgery. Often at its most acute stage in the minutes just before induction, anxiety may even affect the outcome of the surgical procedure.<sup>1</sup>

To relieve anxiety promptly and predictably, no agent is more effective than Injectable Valium® (diazepam/Roche) I.V.

Within minutes after an I.V. injection,<sup>2,3</sup> most patients become noticeably calmer, sedated yet easily aroused if necessary. This response is prompt and predictable—just the kind you want in the anxious moments before surgery.

## Rarely compromises cardiac or respiratory function

Injectable Valium rarely produces clinically significant alterations in basal circulatory parameters.<sup>4,6</sup> In a series of 16,000 patients, apnea occurred in only three patients given Injectable Valium intravenously.<sup>7</sup> However, caution should be taken when administering the agent to elderly or debilitated patients with limited pulmonary reserve. Resuscitative equipment should be available for all patients, and narcotics should be reduced by one-third or more; in some cases they may be eliminated.





# OPERATIVE PERIOD

## to diminish recall

### Diminishes recall of unpleasant or painful procedures

When patients have vivid memories of invasive procedures, they may be less than willing to undergo such procedures again, even if they are medically necessary.<sup>8,9</sup> Recall of procedures such as endotracheal intubation can be diminished by the rapid-acting amnesic effect of Injectable Valium (diazepam/Roche) I.V. Anterograde amnesia usually begins within three minutes after a single I.V. injection, peaks within ten minutes and lasts for 20 to 60 minutes.<sup>3,10,11</sup>

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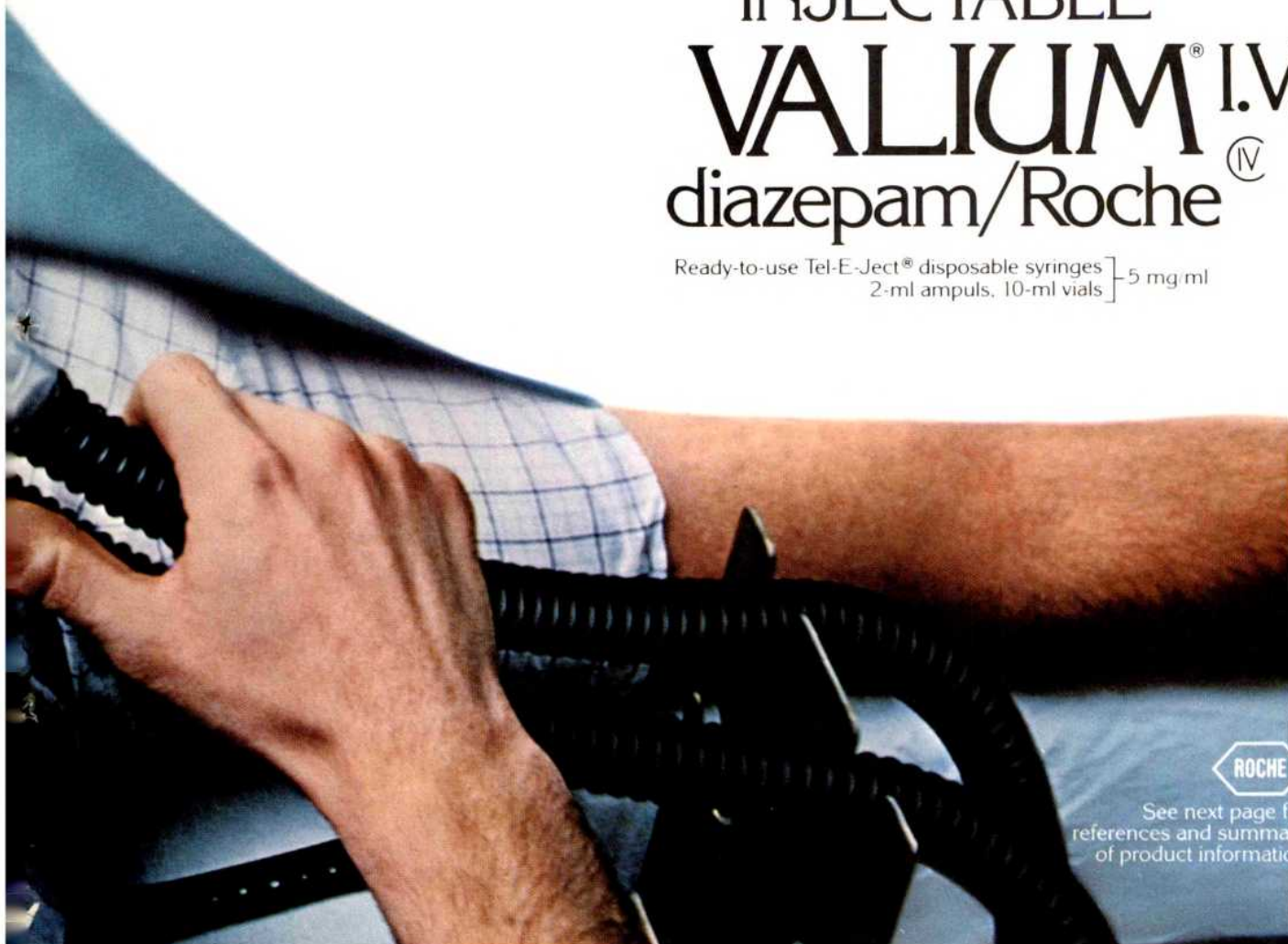
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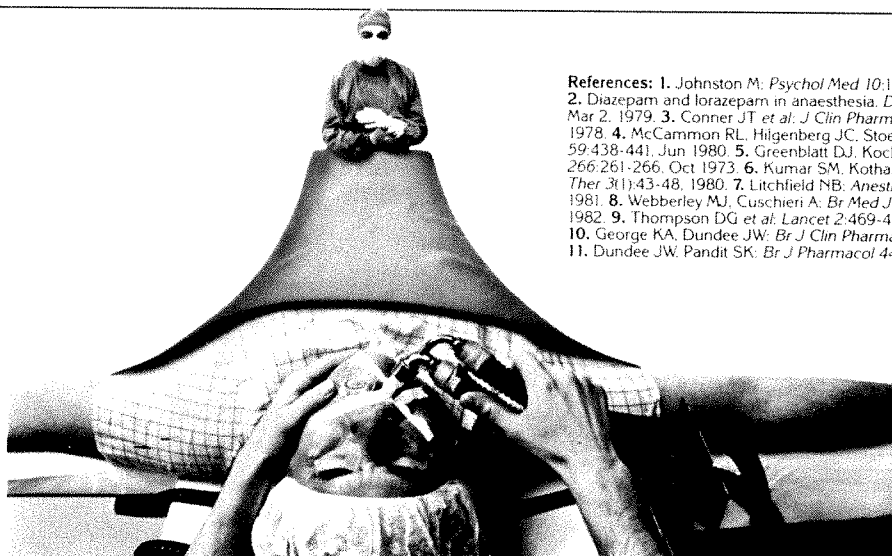
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See next page for  
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- References: 1. Johnston M. *Psychol Med* 10:145-152, Feb 1980.  
 2. Diazepam and lorazepam in anaesthesia. *Drug Ther Bull* 17:19-20, Mar 2, 1979. 3. Conner JT et al. *J Clin Pharmacol* 18:285-292, May-Jun 1978. 4. McCammon RL, Hilgenberg JC, Stoelting RK. *Anesth Analg* 59:438-441, Jun 1980. 5. Greenblatt DJ, Koch-Weser J. *Am J Med Sci* 266:261-266, Oct 1973. 6. Kumar SM, Kothary SP, Zsigmond EK. *Clin Ther* 3(1):43-48, 1980. 7. Litchfield NB. *Anesth Prog* 29:11-17, Jan-Feb, 1981. 8. Webberley MJ, Cuschieri A. *Br Med J* 285:251-252, Jul 24, 1982. 9. Thompson DG et al. *Lancet* 2:469-470, Aug 30, 1980.  
 10. George KA, Dundee JW. *Br J Clin Pharmacol* 4:45-50, Feb 1977.  
 11. Dundee JW, Pandit SK. *Br J Pharmacol* 44:140-144, Jan 1972.

## INJECTABLE VALIUM® (diazepam/Roche) ©

Please consult complete product information, a summary of which follows:

**Indications:** Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

**Contraindications:** Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

**Warnings:** To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling and, rarely, vascular impairment when used IV: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly IV, it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least 1/3, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

**Usage in Pregnancy:** Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

**Precautions:** Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds, which may potentiate action of Valium (diazepam/Roche), i.e., phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

**Adverse Reactions:** Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoaesthesia, slurred speech, syncope, tremor, vertigo, constipation, nausea,

incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

**Dosage:** Usual initial dose in older children and adults is 2 to 20 mg I.M. or IV, depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

**I.M. use:** by deep injection into the muscle.

**IV use:** inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly IV, it may be injected slowly through the infusion tubing as close as possible to the vein insertion. Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or IV, and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or IV, repeat in 3 to 4 hours if necessary; acute alcohol withdrawal, 10 mg I.M. or IV, initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or IV, initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, administer IV, slowly; for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or IV, repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (IV route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary, keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (IV preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow IV preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate IV dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if IV cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg IV within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

**Management of Overdosage:** Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, IV fluids, adequate airway. Hypotension may be combated by the use of levaterenol or metaraminol. Dialysis is of limited value.

**Supplied:** Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1 and 10; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.



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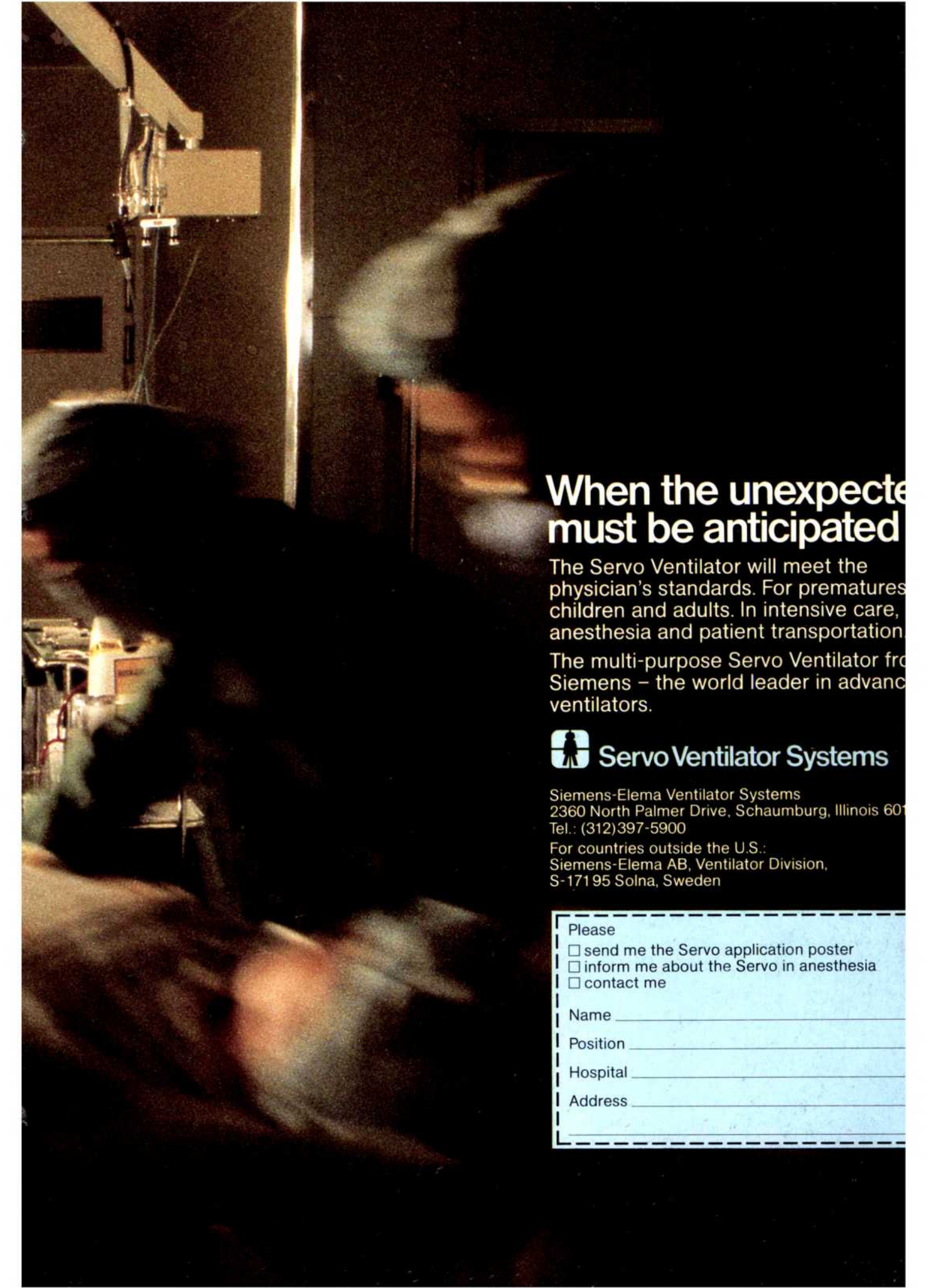
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See important information on following page.

# ATIVAN® (LORAZEPAM) INJECTION IM or IV

**DESCRIPTION:** Ativan® (lorazepam) injection, a benzodiazepine with anxiolytic and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

**CLINICAL PHARMACOLOGY:** IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

**INDICATIONS AND USAGE:** In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

**CONTRAINDICATIONS:** Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

**WARNINGS:** PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION. THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

**Pregnancy:** LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chloridiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

**Endoscopic Procedures:** There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

**PRECAUTIONS: General:** Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE AND ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

**Information for Patients:** As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

**Laboratory Tests:** In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

**Drug Interactions:** Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

**Drug/Laboratory Test Interactions:** No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

**Pregnancy:** Pregnancy Category D. See WARNINGS section.

**Labor and Delivery:** There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

**Nursing Mothers:** Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

**Pediatric Use:** There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

**ADVERSE REACTIONS: CNS:** Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE AND ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

**Local Effects:** IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.6% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately post-injection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

**Cardiovascular System:** Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

**Respiratory System:** Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

**Other Adverse Experiences:** Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

**DRUG ABUSE AND DEPENDENCE:** As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

**OVERDOSE:** Overdose of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdose is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

**DOSAGE AND ADMINISTRATION:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

**Intramuscular Injection:** For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure. Administer narcotic analgesics at least preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

**Intravenous Injection:** For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure. EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

**Administration:** When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP; Sodium Chloride Injection, USP; 5% Dextrose Injection, USP.

**HOW SUPPLIED:** Ativan® (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.  
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For IM or IV injection.

Protect from light. Keep in refrigerator.

**Directions for Dilution for IV Use:** To dilute, adhere to following procedure: (1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

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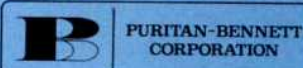


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PRESERVATIVE-FREE<sup>®</sup>  
**Duramorph PF**  
(morphine sulfate injection, USP) CII

# creates new options in pain management

## 1 **DURAMORPH<sup>®</sup> PF provides profound site-selective analgesia.**

DURAMORPH<sup>®</sup> PF delivers preservative-free morphine directly to localized opiate receptors in the spinal cord, selectively blocking nociceptive impulse transmission to the brain's pain centers.

## 2 **DURAMORPH<sup>®</sup> PF prevents postoperative pain when administered at the completion of surgery.**

A single 5 mg epidural injection before the onset of postoperative pain provides pain relief associated with many obstetric/gynecologic, orthopedic, thoracic, and abdominal procedures. Use of DURAMORPH<sup>®</sup> PF is particularly convenient when an epidural catheter is already in place for operative anesthesia.

***“From a humanitarian viewpoint, epidural morphine could be considered the ideal postoperative analgesic . . .”<sup>1</sup>***

#### References:

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### **Guidelines for Administration of DURAMORPH<sup>®</sup> PF**

- The epidural route should be used whenever possible; intrathecal administration has been associated with greater potential for immediate or delayed adverse effects.
- Administration should be limited to the lumbar region whenever possible; thoracic injection has been shown to dramatically increase the incidence of respiratory depression.
- Predisposing factors in morphine-related respiratory depression include: thoracic administration,<sup>4</sup> advanced age,<sup>4</sup> reduced ventilatory capacity,<sup>5</sup> high doses,<sup>6</sup> concomitant administration of opioids,<sup>5</sup> supine body position,<sup>7</sup> CNS depressants,<sup>5</sup> and raised intrathoracic pressure.<sup>8</sup> Careful selection of patients, avoidance of opiate premedication, and maintenance of patients in a head-up position may minimize the occurrence of respiratory depression.

**See complete prescribing information**



### **3** DURAMORPH® PF relieves pain for up to 24 hours with a single epidural injection.

DURAMORPH® PF provides extended pain protection with a duration of analgesic effect that is nearly four times longer than that of conventional systemic narcotics (IV morphine).<sup>1</sup>

### **4** DURAMORPH® PF is associated with a low incidence of respiratory depression.

Delayed respiratory depression has been reported; patient monitoring should be continued for at least 24 hours after each dose. Naloxone reverses respiratory depression without diminishing analgesia.

### **5** DURAMORPH® PF maintains patient comfort with virtually no sedation, or loss of motor or sympathetic function.

DURAMORPH® PF out-performs conventional systemic narcotics and local anesthetics in producing site-selective analgesia. Patients are alert and more active participants in their nursing and rehabilitative care.

### **6** DURAMORPH® PF promotes early ambulation and reduces postoperative complications.

Patients receiving DURAMORPH® PF frequently become ambulatory earlier than patients receiving conventional systemic narcotics—often in as little as half the time<sup>1</sup>—which may reduce the risk of postoperative respiratory and thromboembolic complications.<sup>3</sup>

*“Due to absence of sedation and the lack of orthostatic hypotension, high risk patients . . . ambulate early leading to decreased risk for postoperative thromboembolic and respiratory complications.”<sup>2</sup>*

### **7** DURAMORPH® PF may hasten patient recovery and shorten hospital stays.

In a study of patients at high risk of postoperative complications, epidural morphine shortened hospital stays after elective gastropasty from an average of 9 days to 7 days.<sup>3</sup>

### **8** DURAMORPH® PF may mean cost savings in postoperative care.

The benefits of early ambulation, greater patient cooperation with nursing/rehabilitative care, fewer postoperative complications, and shortened hospital stays—offset against the moderately increased costs of short-term postoperative monitoring—may result in a significant net savings in the costs of medical care, an important consideration for institutions dependent on fixed-cost reimbursement policies.

*“... effective analgesia, early ambulation, early normalization of gastrointestinal function, and minimal respiratory complications in the postoperative period all contributed to a shorter hospitalization time in patients receiving epidural morphine analgesia.”<sup>3</sup>*



# PRESERVATIVE-FREE<sup>®</sup> Duramorph<sup>®</sup> PF (morphine sulfate injection, USP) CII

## DESCRIPTION

Preservative-free DURAMORPH<sup>®</sup> PF (Morphine Sulfate Injection, USP) is a sterile, pyrogen-free, isobaric solution free of antioxidants, preservatives or other potentially neurotoxic additives, and is intended for intravenous, epidural or intrathecal administration as a narcotic analgesic. Each milliliter contains morphine sulfate 0.5 mg or 1 mg (Warning: May Be Habit Forming) and sodium chloride 9 mg in Water for Injection. pH range is 2.5-6.0. Ampuls are sealed under nitrogen. Each Dosette<sup>®</sup> ampul is intended for SINGLE USE ONLY. Discard any unused portion. DO NOT AUTOCLAVE.

## INDICATIONS AND USAGE

Preservative-free DURAMORPH<sup>®</sup> PF is a systemic narcotic analgesic for administration by the intravenous, epidural or intrathecal routes. It is used for the management of pain not responsive to non-narcotic analgesics. Morphine sulfate, administered epidurally or intrathecally, provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.

## CONTRAINDICATIONS

DURAMORPH<sup>®</sup> PF is contraindicated in those medical conditions which would preclude the administration of opioids by the intravenous route—allergy to morphine or other opiates, acute bronchial asthma, upper airway obstruction.

Administration of morphine by the epidural or intrathecal route is contraindicated in the presence of infection at the injection site, anticoagulant therapy, bleeding diathesis, parenterally administered corticosteroids within a two week period or other concomitant drug therapy or medical condition which would contraindicate the technique of epidural or intrathecal analgesia.

## WARNINGS

DURAMORPH<sup>®</sup> PF administration should be limited to use by those familiar with the management of respiratory depression, and in the case of epidural or intrathecal administration, familiar with the techniques and patient management problems associated with epidural or intrathecal drug administration. Because epidural administration has been associated with lessened potential for immediate or late adverse effects than intrathecal administration, the epidural route should be used whenever possible. Rapid intravenous administration may result in chest wall rigidity.

FACILITIES WHERE DURAMORPH<sup>®</sup> PF IS ADMINISTERED MUST BE EQUIPPED WITH RESUSCITATIVE EQUIPMENT, OXYGEN, NALOXONE INJECTION, AND OTHER RESUSCITATIVE DRUGS. WHEN THE EPIDURAL OR INTRATHECAL ROUTE OF ADMINISTRATION IS EMPLOYED, PATIENTS MUST BE OBSERVED IN A FULLY EQUIPPED AND STAFFED ENVIRONMENT FOR AT LEAST 24 HOURS.

SEVERE RESPIRATORY DEPRESSION UP TO 24 HOURS FOLLOWING EPIDURAL OR INTRATHECAL ADMINISTRATION HAS BEEN REPORTED.

Morphine sulfate may be habit forming. (See Drug Abuse and Dependence section.)

## PRECAUTIONS

### GENERAL

Preservative-free DURAMORPH<sup>®</sup> PF (Morphine Sulfate Injection, USP) should be administered with extreme caution in aged or debilitated patients, in the presence of increased intracranial intraocular pressure and in patients with head injury. Pupillary changes (miosis) may obscure the course of intracranial pathology. Care is urged in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis). Seizures may result from high doses. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.

It is recommended that administration of DURAMORPH<sup>®</sup> PF by the epidural or intrathecal routes be limited to the lumbar area. Intrathecal use has been associated with a higher incidence of respiratory depression than epidural use.

Smooth muscle hypertonicity may result in biliary colic, difficulty in urination and possible urinary retention requiring catheterization. Consideration should be given to risks inherent in urethral catheterization, e.g., sepsis, when epidural or intrathecal administration is considered, especially in the perioperative period.

Elimination half-life may be prolonged in patients with reduced metabolic rates and with hepatic or renal dysfunction. Hence, care should be exercised in administering morphine in these conditions, particularly with repeated dosing.

Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be observed carefully for orthostatic hypotension, particularly in transport.

Patients with chronic obstructive pulmonary disease and patients with acute asthmatic attack may develop acute respiratory failure

with administration of morphine. Use in these patients should be reserved for those whose conditions require endotracheal intubation and respiratory support or control of ventilation.

## DRUG INTERACTIONS

Depressant effects of morphine are potentiated by either concomitant administration or in the presence of other CNS depressants such as alcohol, sedatives, antihistamines or psychotropic drugs (e.g., MAO inhibitors, phenothiazines, butyrophenones and tricyclic antidepressants). Premedication or intra-anesthetic use of neuroleptics with morphine may increase the risk of respiratory depression.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**  
Studies of morphine sulfate in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

## PREGNANCY

**Teratogenic effects—Pregnancy Category C.** Animal reproduction studies have not been conducted with morphine sulfate. It is also not known whether morphine sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Morphine sulfate should be given to a pregnant woman only if clearly needed.

**Nonteratogenic effects.** Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

## LABOR AND DELIVERY

Intravenous morphine readily passes into the fetal circulation and may result in respiratory depression in the neonate. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the neonate. In addition, intravenous morphine may reduce the strength, duration and frequency of uterine contraction resulting in prolonged labor.

**Epidurally and intrathecally administered morphine** readily passes into the fetal circulation and may result in respiratory depression of the neonate. Controlled clinical studies have shown that epidural administration has little or no effect on the relief of labor pain.

However, studies have suggested that in most cases 0.2 to 1 mg of morphine intrathecally provides adequate pain relief with little effect on the duration of first stage labor. The second stage labor, though, may be prolonged if the parturient is not encouraged to bear down. A continuous intravenous infusion of naloxone, 0.6 mg/hr, for 24 hours after intrathecal injection may be employed to reduce the incidence of potential side effects.

## NURSING MOTHERS

Morphine is excreted in maternal milk. Effect on the nursing infant is not known.

## PEDIATRIC USE

Safety and effectiveness in children have not been established.

## ADVERSE REACTIONS

The most serious side effect is respiratory depression. Because of

delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing. Bolus administration by the epidural or intrathecal route may result in early respiratory depression due to direct venous redistribution of morphine to the respiratory centers in the brain. Late (up to 24 hours) onset of acute respiratory depression has been reported with administration by the epidural or intrathecal route and is believed to be the result of rostral spread. Reports of respiratory depression following intrathecal administration have been more frequent, but the dosage used in most of these cases has been considerably higher than that recommended. This depression may be severe and could require intervention (See Warnings and Overdose sections). Even without clinical evidence of ventilatory inadequacy, a diminished CO<sub>2</sub> ventilation response may be noted for up to 22 hours following epidural or intrathecal administration.

While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulating catecholamines. Excitation of the central nervous system resulting in convulsions may accompany high doses of morphine given intravenously. Dysphoric reactions may occur and toxic psychoses have been reported.

Epidural or intrathecal administration is accompanied by a high incidence of pruritus which is dose related but not confined to site of administration. Nausea and vomiting are frequently seen in patients following morphine administration. Urinary retention which may persist for 10-20 hours following single epidural or intrathecal administration has been reported in approximately 90% of males. Incidence is somewhat lower in females. Patients may require catheterization (see Precautions). Pruritus, nausea, vomiting and urinary retention frequently can be alleviated by the intravenous administration of low doses of naloxone (0.2 mg).

Tolerance and dependence to chronically administered morphine, by whatever route, is known to occur (see Drug Abuse and Dependence section).

Miscellaneous side effects include constipation, headache, anxiety, depression of cough reflex, interference with thermal regulation and oliguria. Evidence of histamine release such as urticaria, wheals and/or local tissue irritation may occur.

In general, side effects are amenable to reversal by narcotic antagonists. NALOXONE INJECTION AND RESUSCITATIVE EQUIPMENT SHOULD BE IMMEDIATELY AVAILABLE FOR ADMINISTRATION IN CASE OF LIFE-THREATENING OR INTOLERABLE SIDE EFFECTS.

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance:** Morphine sulfate is a Schedule II substance under the Drug Enforcement Administration classification.

**Abuse:** Morphine has recognized abuse potential.

**Dependence:** Cerebral and spinal receptors may develop tolerance/dependence independently, as a function of local dosage. Care must be taken to avert withdrawal in those patients who have been maintained on parenteral/oral narcotics when epidural or intrathecal administration is considered. Withdrawal may occur following chronic epidural or intrathecal administration, as well as the development of tolerance to morphine by these routes. (See Nonteratogenic effects under Pregnancy.)

## OVERDOSAGE

Overdosage is characterized by respiratory depression with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory center or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone, is a specific antidote. Naloxone (usually 0.4 mg) should be administered intravenously, simultaneously with respiratory resuscitation. As the duration of effect of naloxone is considerably shorter than that of epidural or intrathecal morphine, repeated administration may be necessary. Patients should be closely observed for evidence of reanarctization. **Note:** Respiratory depression may be delayed in onset up to 24 hours following epidural or intrathecal administration. In painful conditions, reversal of narcotic effect may result in acute onset of pain and release of catecholamines. Careful administration of naloxone may permit reversal of side effects without affecting analgesia. Parenteral administration of narcotics in patients receiving epidural or intrathecal morphine may result in overdosage.

## HOW SUPPLIED

Amber Dosette<sup>®</sup> ampuls for intravenous, epidural and intrathecal administration.

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# The premedication that well into the

## Before Surgery

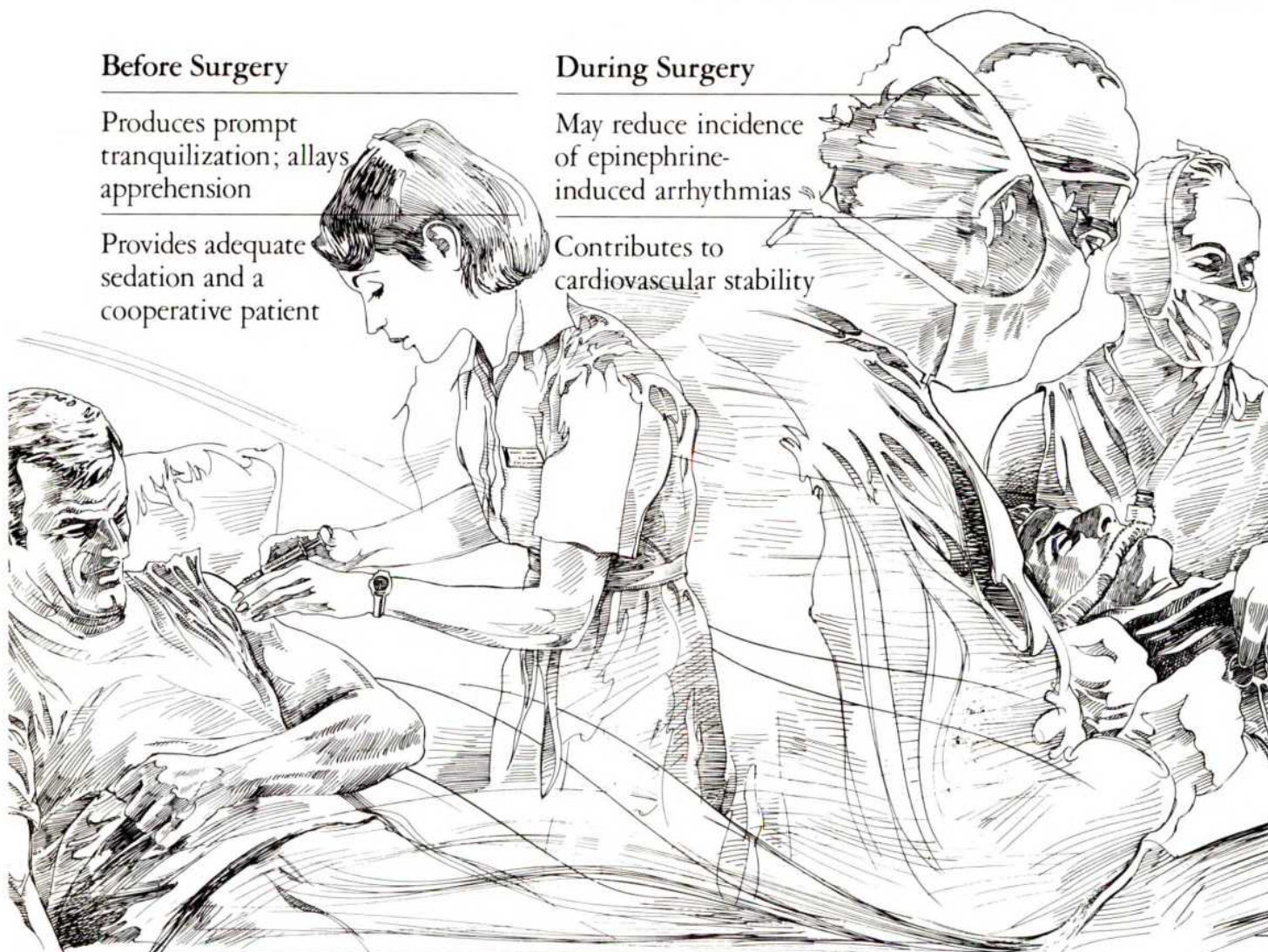
Produces prompt tranquilization; allays apprehension

Provides adequate sedation and a cooperative patient

## During Surgery

May reduce incidence of epinephrine-induced arrhythmias

Contributes to cardiovascular stability



Before prescribing please consult complete prescribing information, of which the following is a brief summary.

### DESCRIPTION:

2 ml. and 5 ml. ampoules

Each ml. contains:

Droperidol ..... 2.5 mg.

Lactic acid for pH adjustment to  $3.4 \pm 0.4$

10 ml. vials

Each ml. contains:

Droperidol ..... 2.5 mg.

With 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to  $3.4 \pm 0.4$ .

Protect from light. Store at room temperature.  
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY  
Droperidol is a neuroleptic (tranquilizer) agent.

### INDICATIONS:

INAPSINE (droperidol) is indicated: to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

**CONTRAINDICATIONS:** INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

**WARNINGS:** FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received

INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as  $\frac{1}{4}$  to  $\frac{1}{2}$  those usually recommended.

**PRECAUTIONS:** The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is

used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

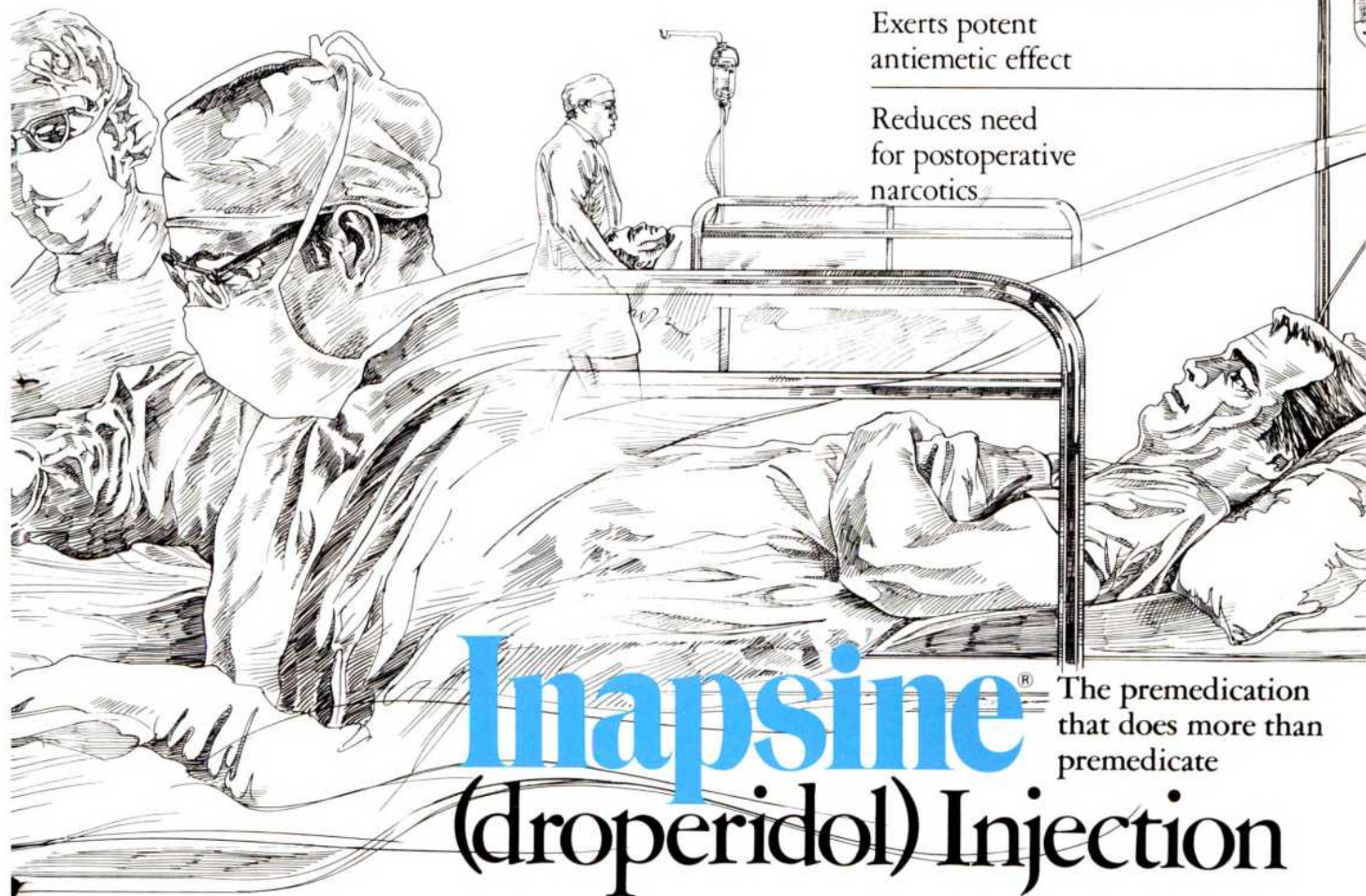
If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.



# goes on helping... postoperative period



## After Surgery

Exerts potent  
antiemetic effect

Reduces need  
for postoperative  
narcotics

## Inapsine<sup>®</sup> (droperidol) Injection

The premedication  
that does more than  
premedicate

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.<sup>9</sup>

**ADVERSE REACTIONS:** The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression,

apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur.

Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

**DOSAGE AND ADMINISTRATION:** Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

### Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

### II. Adjunct to General Anesthesia

Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.

Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

If INNOVAR<sup>®</sup> injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

**How Supplied:** 2 ml. and 5 ml. ampoules—packages of 10; 10 ml. multiple-dose vials—packages of 10.  
U.S. Patent No. 3,161,645  
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10  
March 1980, Revised June 1980

<sup>9</sup>See full prescribing information for complete description.  
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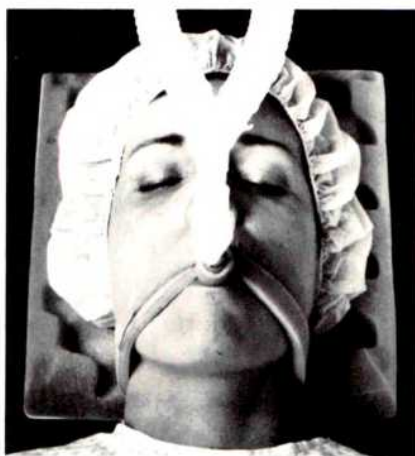
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“Hypoxia is a major cause of morbidity and mortality during anesthesia.”<sup>1</sup>

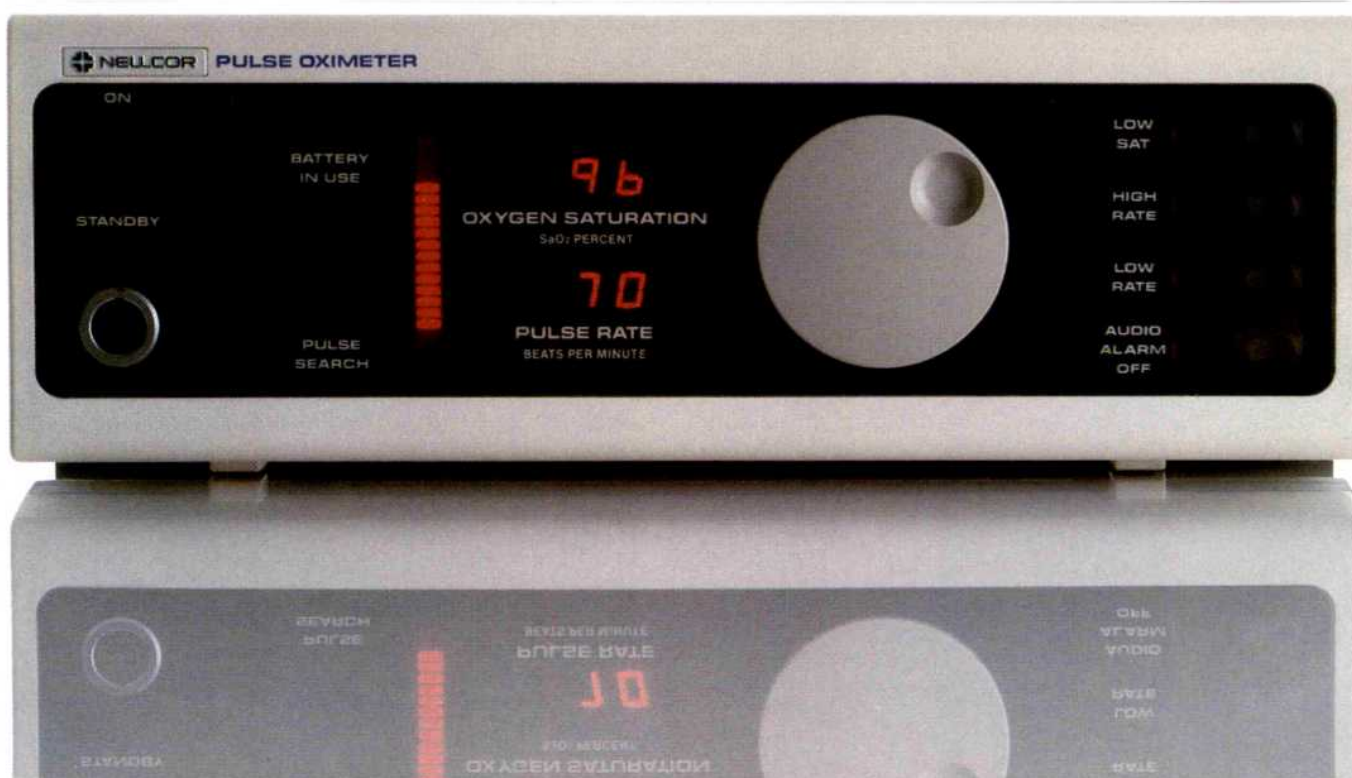
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<sup>1</sup>Flynn M: Hypoxemia Detection During Pediatric Endoscopy. Presented at The American Academy of Pediatrics, 1983, pp 1-2.

<sup>2</sup>Davis DA: An Analysis of Anesthetic Mishaps from Medical Liability Claims. in Pierce EC Jr, Cooper JB (eds): *Analysis of Anesthetic Mishaps*. International Anesthesiology Clinics. Boston: Little, Brown and Company, 1984, Vol 22, No 2, pp 31-42.

<sup>3</sup>Rubsamen DS (ed): Professional Liability Newsletter, 1984, Vol 15, No 6.

<sup>4</sup>Whitcher C, New W Jr, Bacon B: Perianesthetic oxygen saturation vs. skill of the anesthetist. *Anesthesiology* 57: 1982. Suppl to abstract for American Society of Anesthesiologists, October 18, 1982.

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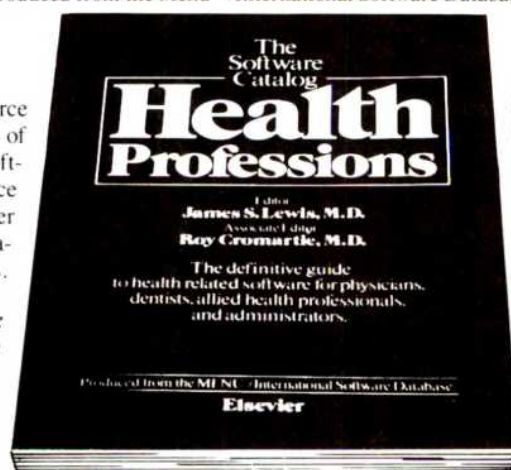
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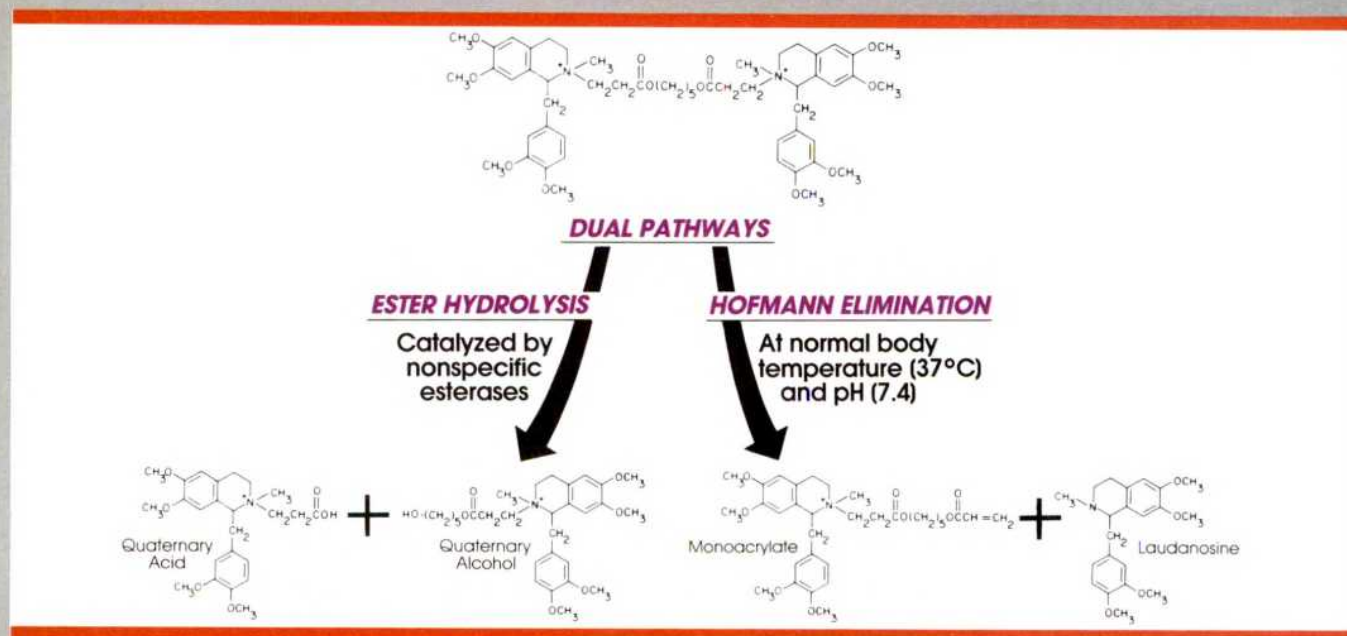
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□ *Tracrium® Injection (atracurium besylate)* is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:

① *Hofmann elimination*—a nonenzymatic process that occurs at physiologic temperature and pH

② *Ester hydrolysis*—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required

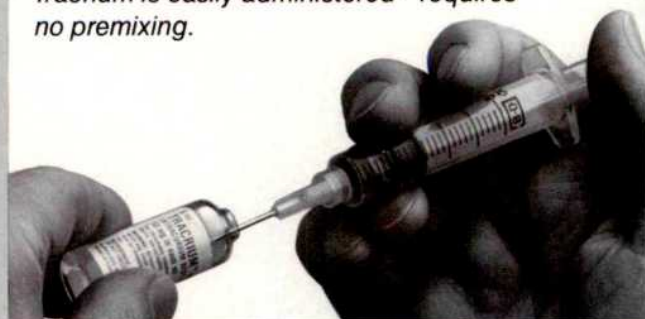
These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."<sup>1</sup>

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."<sup>2</sup>

## Convenient and Ready to Use

Tracrium is easily administered—requires no premixing.

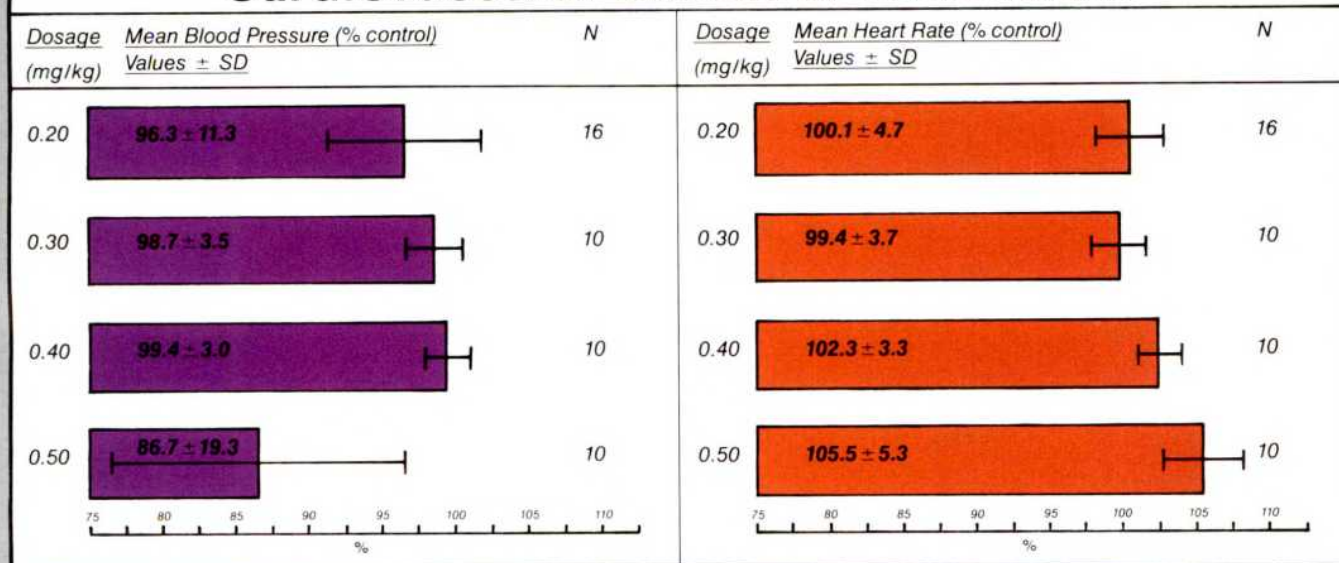




## Few Cardiovascular Effects at Recommended Dosages

☐ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.

### Cardiovascular effects of atracurium



Adapted from Basta et al.<sup>3</sup>

## No Cumulative Effects Upon Recovery, After Multiple Doses

- ☐ Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time
- ☐ Once recovery begins, it is relatively rapid and independent of dose
- ☐ This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."<sup>1</sup>

## Minimal Histamine Release

- ☐ Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine
- ☐ Clinically significant histamine release occurs well within the clinical dosage range (at ED<sub>95</sub>) for curare, at the upper limits of the clinical dosage range (at 2  $\times$  ED<sub>95</sub>) for metocurine and outside the clinical dosage range (at 3  $\times$  ED<sub>95</sub>) for atracurium<sup>4</sup>
- ☐ The lack of hemodynamic changes due to Tracrium suggests minimal histamine release

Please see brief summary of prescribing information on the following page.

#### REFERENCES:

1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. *Seminars in Anesthesia* 1982; 1:57-62.
2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. *Anesth Analg* 1982; 61:730-734.
3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. *Anesth Analg* 1982; 61:723-729.
4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. *Anesthesiology* 1982; 57:A261.

**TRACRIUM® INJECTION**  
(atracurium besylate)



## TRACRIUM® INJECTION (atracurium besylate)

**DESCRIPTION:** Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

**INDICATIONS AND USAGE:** Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it.

**WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebation. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

### PRECAUTIONS:

**General:** Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered, however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Pregnancy: Teratogenic Effects:** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been

administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 2 years have not been established.

**ADVERSE REACTIONS:** Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

In the United Kingdom, where Tracrium has been marketed since December, 1982, the most frequent adverse reactions reported in association with the use of Tracrium are cutaneous histamine-like reactions, bronchospasm, and bradycardia. These have been reported to occur in about one in 10,000 patients. Less frequent adverse reactions are hypotension, heart arrest, tachycardia, cyanosis, and apnea, which have been reported to occur in approximately one in 100,000 patients.

**DOSAGE AND ADMINISTRATION:** Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

**HOW SUPPLIED:** Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10). Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4179507

Printed in U.S.A.

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Burroughs Wellcome Co.  
Research Triangle Park  
North Carolina 27709

# TRACRIUM® INJECTION

(atracurium besylate)



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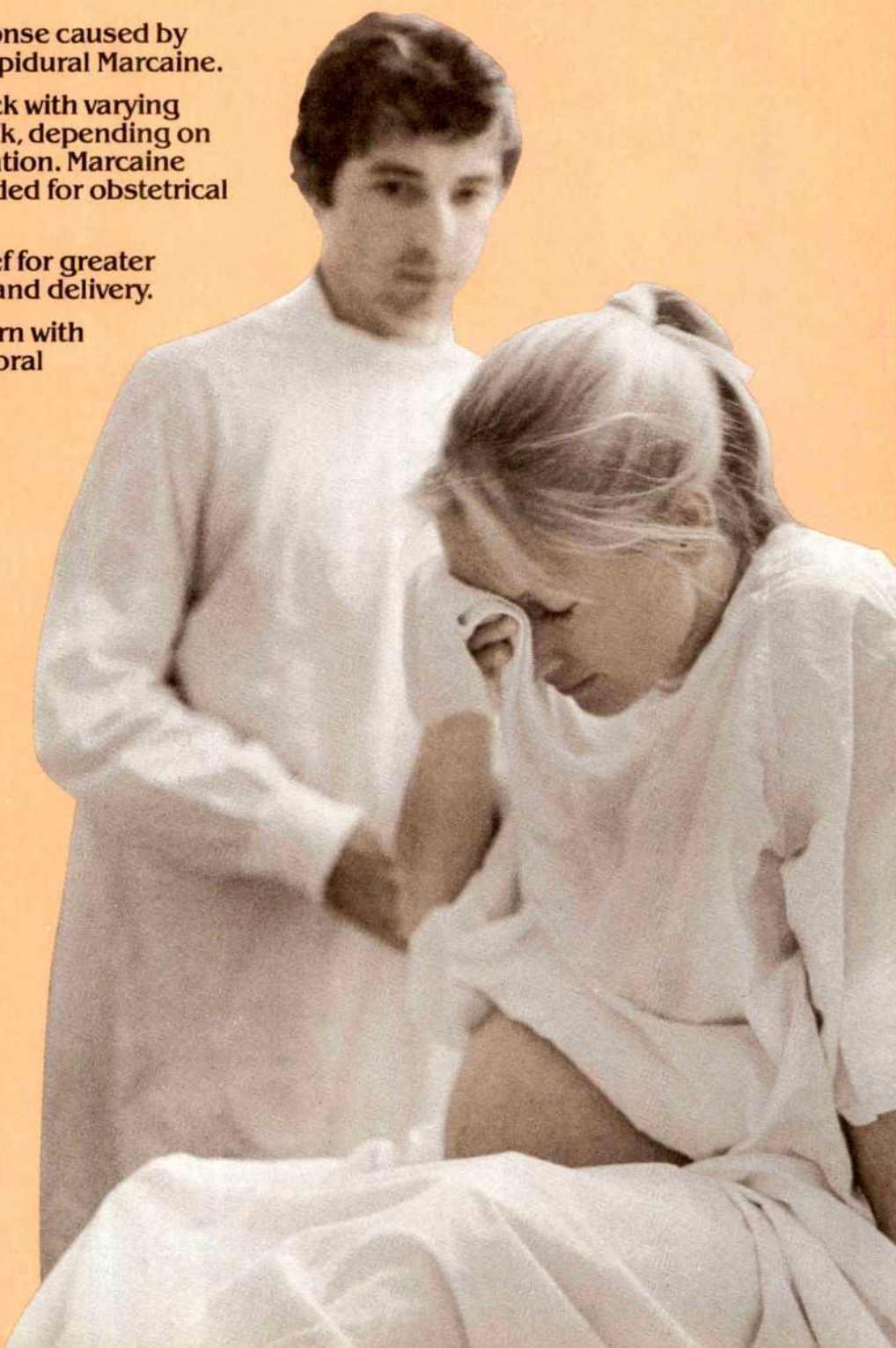
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**CONTRAINDICATIONS:** Obstetric paracervical block anesthesia: use in this technique has resulted in fetal bradycardia and death. Known hypersensitivity to the drug or to any amide-type local anesthetic, or to other components of MARCAINE solutions

## WARNINGS

**THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY. PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY.**

**LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS, PRECAUTIONS AND OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.**

Local anesthetic solutions containing antimicrobial preservatives, ie, those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because their safety has not been established with regard to intrathecal injection—intentionally or not.

It is essential that aspiration for blood or cerebrospinal fluid, where applicable, be done prior to injecting any local anesthetic (the original and all subsequent doses) to avoid intravascular or subarachnoid injection, which can occur even with a negative aspiration.

MARCAINE with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, and used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the tricyclic or imipramine types; severe prolonged hypertension may result.

Pending further experience, MARCAINE administration in children younger than 12 years is not recommended. Mixing, or a prior or concurrent use, of any other local anesthetic with MARCAINE cannot be recommended because such use lacks sufficient clinical data.

There have been reports of cardiac arrest and death with MARCAINE for intravenous regional anesthesia (Bier block). Since information on safe dosages and procedural techniques is lacking, MARCAINE is not recommended.

**PRECAUTIONS: General:** Safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, drugs, and oxygen should be available for immediate use. (See WARNINGS, ADVERSE REACTIONS, OVERDOSAGE.) During major regional nerve blocks, the patient should have IV fluids via an indwelling catheter to assure a functioning intravenous pathway. The lowest effective anesthetic dosage should be used to avoid high plasma levels and serious adverse effects.

**Epidural Anesthesia:** The 0.5% and 0.75% solutions should be administered in increments of 3-5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Administration should be slow, with frequent aspirations before and during the procedure to avoid intravascular injection which is still possible even if aspirations for blood are negative. Syringe aspirations should also be performed before and during each supplemental injection by "continuous" (intermittent) catheter technique. During an epidural procedure, it is recommended that a test dose be administered initially and the effects monitored before giving the full dose. When using continuous catheter technique, test doses should be given prior to both the original and all reinforcing doses because plastic tubing in the epidural space can migrate (etc., as in package insert). Clinical conditions permitting, the test dose should contain epinephrine (10-15 µg has been suggested) to provide warning of unintended intravascular injection. If injected into a blood vessel, this amount is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient who may exhibit only a pulse-rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, heart rate should be monitored for any increase. Patients on beta blockers may not manifest such changes, but blood-pressure monitoring can detect a transient systolic rise. The test dose should also contain 10-15 µg of MARCAINE or an equivalent amount of another local anesthetic to detect unintended intrathecal injection. This will be evidenced within a few minutes by signs of spinal block (eg, decreased gluteal sensation, paresis of the legs or in the sedated patient, absent knee jerk). Two or 3 mL of MARCAINE 0.5% with epinephrine 1:200,000 contain, respectively, 10 and 15 mg of bupivacaine HCl and 10 and 15 µg of epinephrine. An intravascular or subarachnoid injection is still possible even with negative results of the test dose, which itself may produce an epinephrine-induced cardiovascular or systemic toxic reaction or high spinal effect.

Repeated doses may cause significant increases in plasma levels with each such injection due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the patient's status. Debilitated, elderly, and acutely ill patients should be given reduced doses commensurate with age and physical status. Also use local anesthetics with caution in patients with hypotension or heart block.

There should be careful and constant monitoring of the patient's cardiovascular and respiratory (adequacy of ventilation) vital signs and state of consciousness after each injection, and kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching depression, or drowsiness may be warnings of CNS toxicity.

Local anesthetic solutions with a vasoconstrictor should be used cautiously and carefully in body areas supplied by end arteries or with otherwise restricted blood supply (digits, nose, external ear, penis, etc.). Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response; ischemic injury or necrosis may result.

Amide-type anesthetics such as MARCAINE are metabolized by the liver; these drugs (especially repeat doses) should be used cautiously in patients with hepatic disease. Because of an inability to metabolize local anesthetics normally, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations. Also use with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the drug's prolongation of A-V conduction.

Serious dose-related cardiac arrhythmias may occur if preparations containing epinephrine are employed in patients during or following administration of potent inhalation anesthetics. In deciding whether to use these agents concurrently, their combined action on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection should be taken into account (when applicable).

Many drugs used in anesthesia conduct are potentially triggering agents for familial malignant hyperthermia. Because it is unknown whether amide-type anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard management protocol be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s), and prompt treatment including oxygen, dantrolene IV (see prescribing information before use), and other supportive measures.

**Use in Head and Neck Area:** Small doses of local anesthetics injected into the area, including retrobulbar, dental, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported and may be due to intraarterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored constantly, with resuscitative equipment and personnel immediately available if needed. Do not exceed dosage recommendations. (See DOSAGE AND ADMINISTRATION.)

**Use in Ophthalmic Surgery:** With MARCAINE 0.75% for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Presence of akinesia alone determines readiness for surgery.

**Use in Dentistry:** Because of the long duration of anesthesia when MARCAINE 0.5% with epinephrine is used dentally, caution patients about inadvertent trauma to tongue, lips, and buccal mucosa; advise them not to chew solid foods or test the anesthetized area by biting or probing until anesthesia has worn off (up to 7 hours).

**Information for Patients:** When appropriate, inform them in advance of possible temporary loss of sensation and motor activity (usually in the lower body) following administration of caudal or epidural anesthesia, or of the possible adverse occurrence noted in package insert.

**Clinically Significant Drug Interactions:** Administering local anesthetic solutions containing epinephrine or norepinephrine to patients receiving MAO inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Thus concurrent use should generally be avoided, in situations when such therapy is necessary, careful monitoring is essential. Concurrent use of vasopressor and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accident. Phenothiazines and butyrophenones may reduce or reverse epinephrine's pressor effect.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term studies in animals of most local anesthetics including bupivacaine have not been conducted. There is no evidence from human data that MARCAINE may be carcinogenic or mutagenic or that it impairs fertility.

**Pregnancy Category C:** Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine was administered to either in doses comparable to 5 to 9 times the maximum recommended daily human dose (400 mg). There are no adequate and well-controlled studies in pregnant women of the drug's effect on fetal development, and potential fetal risk must be justified by potential benefit. This does not exclude use of MARCAINE at term for obstetric anesthesia or analgesia. (See Labor and Delivery.)

**Labor and Delivery:** SEE BOXED WARNING REGARDING OBSTETRIC USE OF 0.75% MARCAINE, and its contraindication in obstetric paracervical block. Local anesthetics cross the placenta rapidly and, when used for epidural, caudal, or pudendal block, can cause varying degrees of maternal, fetal, and neonatal toxicity. (See Pharmacokinetics in CLINICAL PHARMACOLOGY.) The incidence and degree of toxicity depend upon the procedure performed, and drug type, amount, and technique of administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the CNS, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and left-side positioning will help prevent decrease in blood pressure. Fetal heart rate should be monitored continuously, preferably electronically. Epidural, caudal, or pudendal anesthesia may alter parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong second-stage labor by removing the parturient's reflex urge to bear down, or by interference with motor function. Use of obstetric anesthesia may increase need for forceps assistance.

Some local anesthetic drugs may diminish muscle strength and tone for the first day or two of life. It is unreported with bupivacaine.

Of extreme importance: Avoid aortocaval compression of the gravid uterus during administration of regional block. To do this, maintain the parturient in the left lateral decubitus position, or place a blanket roll or sandbag beneath the right hip to displace the gravid uterus away from the great vessels.

**Nursing Mothers:** It is not known whether local anesthetics are excreted in human milk, because many drugs are, administer with caution.

**Pediatric Use:** Without further experience in children under 12, MARCAINE is not recommended for this group.

**ADVERSE REACTIONS:** A major cause of adverse reactions to amide-type local anesthetics is excessive plasma levels, possibly due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

**Systemic:** The most common acute experiences, demanding immediate countermeasures, involve the CNS and cardiovascular systems. Adverse events are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or unintentional intravascular injection of the solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection during performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea. Also, hypotension due to loss of sympathetic tone, and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia, may occur, leading to secondary cardiac arrest if untreated. Factors influencing plasma protein binding such as acidosis, systemic diseases which alter protein production or competition of other drugs for protein binding sites, may diminish individual tolerance.

**Central Nervous System:** Excitation and/or depression, restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly convulsions. Excitement may be transient, depression being the first manifestation of an adverse reaction. Drowsiness merging into unconsciousness and respiratory arrest may quickly follow. Other CNS effects may be nausea, vomiting, chills, pupillary constriction. Incidence of convulsions varies with the procedure used and total dose administered. In studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of procedures.

**Cardiovascular:** High doses of unintentional intravascular injection may lead to high plasma levels and related myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. (See WARNINGS, PRECAUTIONS, OVERDOSAGE.)

**Allergic:** Rare, and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. Possible reactions: urticaria, pruritus, erythema, angioneurotic edema (including laryngeal), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, perhaps anaphylactoid symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type anesthetic group reported; value of sensitivity screening is unestablished.

**Neurologic:** Incidence of adverse reactions associated with use of such drugs may be related to the total dose administered, and dependent upon the particular drug use, route of administration, and the patient's physical status. Many effects may be related to technique, with or without the drug being contributory.

In performing caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and physiologic and physical effects of dural puncture. High spinal is characterized by leg paralysis, loss of consciousness, respiratory paralysis, and bradycardia. Effects following epidural or caudal anesthesia may include spinal block of varying magnitude (including high or total spinal block), hypotension secondary to spinal block, urinary retention, fecal and urinary incontinence, loss of perineal sensation and sexual function, persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities, and loss of sphincter control—all of which may show slow, incomplete, or no recovery; headache, backache, aseptic meningitis, meningism, slowing of labor, increased incidence of forceps delivery, cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

**OVERDOSAGE:** Acute emergency during therapeutic local anesthesia is generally related to high plasma levels or unintended subarachnoid injection of the solution. (See ADVERSE REACTIONS, WARNINGS, PRECAUTIONS.)

The first consideration in management is prevention, best accomplished by careful, constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each injection. At the first sign of change, administer oxygen. This measure may prevent convulsions if they have not already occurred. In systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, give immediate attention to establishing and maintaining a patent airway and controlled ventilation with 100% oxygen (the delivery system must permit instant positive airway pressure by mask). Endotracheal intubation may be indicated to meet the need for prolonged ventilatory support or if difficulty is encountered in the maintenance of a patent airway.

If necessary, use drugs to control convulsions. A 50-100 mg bolus IV injection of succinylcholine will paralyze the patient (without CNS or cardiovascular depression) and facilitate ventilation. A 5-10 mg IV bolus of diazepam, or 50-100 mg of thiopental, will permit ventilation and counteract CNS stimulation, but these drugs also depress CNS, respiratory and cardiac function, add to postictal depression, and may cause apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should be administered only by those familiar with use. Immediately after institution of ventilatory measures, circulatory adequacy should be evaluated; supportive treatment may require administration of IV fluids and, when appropriate, a vasopressor dictated by the clinical situation (eg, epinephrine or epinephrine to enhance myocardial contractile force).

Recent clinical data from patients experiencing convulsions induced by local anesthetics demonstrated rapid development of hypoxia, hypercarbia, and acidosis, with bupivacaine, within a minute of onset. These observations suggest that O<sub>2</sub> consumption and CO<sub>2</sub> production are greatly increased during the convulsions and emphasize the importance of immediate ventilation with oxygen, if not treated effectively, convulsions and their complications plus myocardial depression from direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities including apnea may occur, underventilation or apnea due to unintentional subarachnoid injection of the solution may also lead to these signs and cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, prolonged resuscitative effort may determine a successful outcome.

In treating systemic toxicity, maternal hypotension, or fetal bradycardia following regional block, avoid aortocaval compression by the gravid uterus. The supine position is dangerous, etc. (as in insert). (See Labor and Delivery in PRECAUTIONS.)

**Composition of Marcaine Solutions:** 0.25%—each mL contains 2.5 mg bupivacaine; 0.5%—each mL contains 5 mg bupivacaine; 0.75%—each mL contains 7.5 mg bupivacaine. All concentrations contain NaCl for isotonicity in Water for Injection.

In multiple-dose vials, each mL also contains 1 mg methylparaben. With epinephrine, each mL also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 mL monothiolglycerol, 2 mg ascorbic acid, 0.0017 mL 60% sodium lactate, and 0.1 mg edetate calcium disodium.

1. Ostheimer GW: Neurobehavioral effects of local anesthesia and fetal resuscitation. *Reg Anesth* 1981;6:136-145.
2. Naulty JS, Ostheimer G, Datta S, et al: Bupivacaine in breast milk following epidural anesthesia for vaginal delivery. Presented as a scientific poster at the Annual Meeting of the American Society of Regional Anesthesia, Lake Buena Vista, FL, March 23-27, 1983.

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## Nitrous Oxide Does Not Hinder the Repair of Halothane-Induced Hepatic Injury in the Rat

Argyro Fassoulaki, MD, Edmond I. Eger II, MD, Brynte H. Johnson, AB,  
Linda D. Ferrell, MD, Edward A. Smuckler, MD, Michael K. Cahalan, MD, Renee R. Eger,  
and Marilyn H. Harper, MD

FASSOULAKI A, EGER EI II, JOHNSON BH, FERREL LD, SMUCKLER EA, CAHALAN MK, EGER RR, HARPER MH. Nitrous oxide does not hinder the repair of halothane-induced hepatic injury in the rat. *Anesth Analg* 1985;64:465-7.

*Nitrous oxide administration may limit DNA synthesis by inactivating methionine synthetase, and may thus hamper the repair of an injured organ such as the liver. To test this possibility, we pretreated rats with phenobarbital and exposed them to 0.3 MAC halothane in 9% oxygen for 46 min, followed immediately and again 24 hr later by 70% nitrous oxide (0.25 MAC) at an  $F_{I_{O_2}}$  of 0.30 for 2 hr. The results from this group were compared with an anesthetic control group in which 0.35% isoflurane (0.25 MAC) was substituted for the nitrous oxide. Additional groups were*

*given a third exposure to nitrous oxide or isoflurane 48 hr after the halothane exposure. All rats were killed 24 hr after their last anesthetic exposure. A second (nonanesthetic) control group of phenobarbital-pretreated rats received 0.3 MAC halothane in 9% oxygen for 46 min and no anesthetic thereafter. They were killed 24, 48, or 72 hr later. Histologic changes in the livers of rats did not differ among the groups given nitrous oxide, isoflurane, or no additional anesthetic after exposure to halothane alone. Thus neither nitrous oxide nor isoflurane appears to hinder the repair of hepatic injury produced by halothane in the hypoxic rat model.*

**Key Words:** ANESTHETICS, GASES—nitrous oxide. ANESTHETICS, VOLATILE—halothane, isoflurane. ENZYMES—methionine synthetase. LIVER—hepatotoxicity.

In animals and humans, nitrous oxide inactivates methionine synthetase (1-3), an enzyme containing vitamin B<sub>12</sub>. This enzyme catalyzes the transfer of a methyl group from methyltetrahydrofolate to homocysteine to form methionine and tetrahydrofolate. Nitrous oxide inactivates methionine synthetase by oxidizing the cobalt of vitamin B<sub>12</sub>. This oxidation changes vitamin B<sub>12</sub> from an active to an inactive cofactor (4,5). Inactivation of methionine synthetase also may interfere with folate metabolism and thus with the synthesis of thymidine and DNA (6-8). The impairment of DNA synthesis may hinder the repair of injured tissue.

Consistent with this hypothesis, Ross et al. (9) found greater hepatic injury in rats given 86% nitrous oxide and 0.75% halothane than in rats given 86% nitrogen and 0.75% halothane. They found similarly that

administration of 70% nitrous oxide immediately prior to the administration of 86% nitrogen and 0.75% halothane produced more liver injury than the administration of 86% nitrogen and 0.75% halothane without nitrous oxide pretreatment. All animals had received phenobarbital pretreatment to induce liver enzymes. Ross et al. concluded that "nitrous oxide impairs the ability of the liver to withstand and recover from hepatotoxicity induced by halothane under hypoxic conditions."

If the conclusion of Ross et al. is correct, then administration of nitrous oxide after liver injury has been caused by halothane should delay or prevent the repair of the liver. Ross et al. did not test this hypothesis because they administered nitrous oxide either before or during the administration of halothane. Further, they did not study the effect of repeated nitrous oxide administrations. The present study supplies these data.

### Methods

Male Sprague-Dawley rats (Charles River Laboratories) were given food ad libitum and sodium phenobarbital, 1 mg/ml, in their drinking water for four

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days. Rats consuming less than a total of 64 mg of phenobarbital were not studied. Phenobarbital was discontinued for 24 hr before the experiments. During the exposures to anesthetics, the rats were placed in individual Plexiglas tubes with a minimum gas flow through each tube of 1 L/min. Temperature of the animals was monitored with rectal probes and maintained between 36.5 and 38.5°C using ice or infrared heat around the tubes. All rats were peer rats and the four experiments described below were conducted in parallel.

#### Experiment 1 (Nonanesthetic Control Group)

Control rats, pretreated with phenobarbital, were exposed to 0.3 MAC halothane for 46 min with an  $Fi_{O_2}$  0.09 and killed 24, 48, or 72 hr later. In a previous study we had found that exposure of phenobarbital-pretreated rats to 0.3 MAC halothane for 46 min ( $Fi_{O_2}$  0.09) produces hepatic injury that can be detected 24 hr after the exposure in 100% of the animals.

#### Experiment 2 (Anesthetic Control Group)

All animals received 0.3 MAC of halothane for 46 min ( $Fi_{O_2}$  0.09) followed by air for 5 min and then 0.35% isoflurane (0.25 MAC) in 30% oxygen for 2 hr. After these exposures, rats were returned to their cages and were given food and water ad libitum. An additional 2 hr exposure to 0.25 MAC isoflurane was conducted 24 hr later. Animals were killed 48 hr after the exposure to halothane.

#### Experiment 3 (Nitrous Oxide Group)

These rats were treated in the same manner as those in experiment 2 except that 70% nitrous oxide (0.25 MAC) was substituted for the 0.35% isoflurane.

#### Experiment 4

Separate groups of rats were treated as in experiments 2 and 3, except that they underwent an additional 2 hr exposure to nitrous oxide or isoflurane 48 hr later. These animals were killed 72 hr after the exposure to halothane.

In all the experiments, inspired concentrations of halothane and isoflurane were monitored by gas chromatography (flame ionization detector) and a Beckman LB-2 infrared analyzer. Specific inspired concentrations of oxygen were achieved by mixing oxygen with nitrogen or with nitrous oxide (for those rats exposed to nitrous oxide). The inspired oxygen concentrations were monitored using a paramagnetic oxygen analyzer (Beckman E-2) calibrated with oxygen and nitrogen when nitrogen was used, and with oxygen and nitrous oxide when nitrous oxide was used.

Table 1. Effect of Nitrous Oxide vs Isoflurane on Repair of the Rat Liver Injured by Halothane

Treatment	Hours after exposure to halothane	n	Average % of lobule injured <sup>a</sup>
Halothane only	24	12	29.3 ± 2.1
	48	8	14.7 ± 3.0
	72	4	0
Halothane, then nitrous oxide	48	15	7.5 ± 2.5
	72	16	2.6 ± 0.8
Halothane, then isoflurane	48	16	14.5 ± 1.8
	72	16	1.8 ± 0.5

<sup>a</sup>Mean percentage ± SEM.

Slides prepared from liver tissue were arranged in a random sequence and were examined by light microscopy by a pathologist (LDF) who was unaware of treatment given the rats. Each slide was examined for the presence of injury and to determine the average percentage of the liver lobules having injured cells.

Fisher's exact test was used to compare data regarding the incidence of hepatic injury, and analysis of variance to estimate whether significant differences existed among groups in the percentage of liver lobule displaying injury. A *P* value of less than 0.05 was considered statistically significant.

## Results

Neither nitrous oxide nor isoflurane administration delayed the recovery from hepatic injury produced by halothane (Table 1, Fig. 1). At no time of sacrifice did the incidence of hepatic injury or the percentage of liver displaying injury differ significantly in the rats given isoflurane vs nitrous oxide nor did either of these groups of rats differ from the nonanesthetic control rats.

## Discussion

The absence of a difference between the nitrous oxide group and the isoflurane (anesthetic control) group indicates that nitrous oxide does not produce a unique adverse effect on the repair process. This comparison is more important than the one between the nitrous oxide group and the nonanesthetic control group. Had a difference been found between the nitrous oxide group and the nonanesthetic group, it could have been interpreted as the result of anesthesia rather than a specific effect of nitrous oxide (such as inactivation of methionine synthetase.) The absence of a difference between the nitrous oxide or isoflurane groups and the nonanesthetic control group indicates that anesthesia per se does not appreciably limit the repair process after hepatic injury.

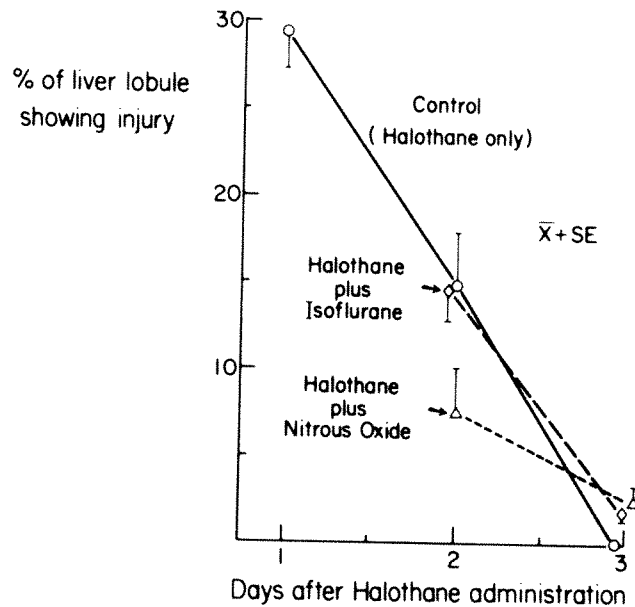


Figure 1. Percentage of rat liver lobule having injured cells after exposure to halothane alone (control,  $\circ$ ), halothane and then nitrous oxide ( $\Delta$ ), or halothane and then isoflurane ( $\diamond$ ) 24, 48, or 72 hr after halothane administration. Values are given as the mean ( $\bar{X}$ ) + SEM.

Our results do not support the hypothesis that nitrous oxide may hinder the repair of liver injury by inactivating methionine synthetase and thereby limiting DNA synthesis. These findings are similar to those of previous investigators who could not demonstrate that nitrous oxide impairs wound healing in rats (10,11).

Our results, however, do not appear to be consistent with those of Ross et al. (9). We have no clear explanation for the apparent differences. The enhancement of halothane-induced liver injury by nitrous oxide appears to require prior or concurrent administration of nitrous oxide. Such prior or concurrent administration may produce cardiorespiratory changes that differ from those that result from administration of nitrous oxide after halothane—as in the present study. Alternatively, the prior or concurrent administration of nitrous oxide may have a more profound effect on methionine synthetase than administration after injury has been produced.

At least two factors may have contributed to our failure and the failure of others to demonstrate that nitrous oxide impairs healing. First, the thesis that nitrous oxide crucially limits DNA synthesis may be wrong. Indeed, an alternative pathway appears to be much more important for such synthesis in rats but not primates. Thus failure may relate to the choice of experimental animal.

Second, although nitrous oxide inactivates methi-

onine synthetase, the rate of repair may be fairly rapid. Koblin et al. (2) found recovery to 70% of control by 24 hr in mice; Deacon et al. (12) reported a slower recovery of the enzyme in rats. Perhaps the amount of remaining and repaired enzyme was sufficient to supply the required DNA. Again, this raises the issue of species differences: is the rate of recovery of the enzyme slower in humans—and would a slower rate of recovery significantly limit DNA synthesis and repair of injured tissues? The rate of inactivation of methionine synthetase by nitrous oxide in humans (3) is slower than in mice; is the rate of recovery also slower? We know that nitrous oxide does impair DNA synthesis in humans (6), but this impaired DNA synthesis may or may not reach a level critical to repair of injured tissues. These untested issues invite further study.

Halothane (Fluothane) for this study was donated by Ayerst Laboratories. Isoflurane (Forane) was donated by Anaquest.

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## Epinephrine Does Not Prolong Lidocaine Spinal Anesthesia in Term Parturients

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SPIVEY DL. Epinephrine does not prolong lidocaine spinal anesthesia in term parturients. *Anesth Analg* 1985;64:468-70.

*The effect of adding epinephrine to spinal anesthesia performed with lidocaine in young, healthy patients was determined in a prospective, controlled, randomized double-blind study. Patients were randomly assigned to one of two groups. One group received lidocaine in dextrose, and the other, lidocaine in dextrose plus epinephrine. Maximum segmental level, time to maximum level, and duration as determined by time to two-segment regression were deter-*

*mined for each of the two groups. There were no significant differences between the two groups in any of the observed parameters, most notably, duration. The present results substantiate those from a previous study in an older population that showed that epinephrine did not significantly prolong lidocaine spinal anesthesia. The present results do not, however, support the hypothesis based upon these earlier data that failure of epinephrine to prolong lidocaine spinal anesthesia is restricted to elderly patients.*

Key Words: ANESTHETIC TECHNIQUES, SPINAL.

For years vasoconstrictor drugs, principally epinephrine, have been added to local anesthetic solutions used for spinal anesthesia in the belief that this prolongs the duration of the anesthesia. This belief has been based upon clinical experience and several early studies that showed that duration was prolonged from 12 to 73% when vasoconstrictors were added (1-3). However, these studies were done under relatively uncontrolled conditions and were not double-blind. A recently published controlled, double-blind study (4) showed that epinephrine does not produce clinically meaningful prolongation of lidocaine spinal anesthesia. Patients in this study underwent transurethral prostatic resection, and one criticism of the study was that the population studied was significantly older than that in previous studies, and might not respond to the epinephrine in the usual way (5). I, therefore, conducted a controlled, double-blind study using a younger patient population to determine whether epinephrine added to lidocaine spinal anesthetic prolonged the duration of the anesthesia.

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### Methods

The study was approved by the Human Studies Committee at Mercy Hospital and Medical Center, San Diego, California. The nature of the study was explained to and informed consent obtained from each patient. Twenty-nine patients were studied. The subjects were young, healthy term gravidas who requested or required low spinal block at delivery. Patients had received varying small doses of narcotic during labor, usually meperidine or alphaprodine with or without promethazine, as determined by the obstetrician. All were prehydrated with at least 1000 ml of Ringer's lactate solution given intravenously. All were placed in the right lateral decubitus position and the subarachnoid space entered with a 26-gauge needle at the L3-4 intervertebral space. Solutions injected were as follows: lidocaine (Astra) 5% in dextrose 7.5%, 0.8 ml (40 mg) with either 0.2 ml of 1:1000 epinephrine (0.2 mg) ( $n = 15$ ) (Astra) or 0.2 ml of normal saline ( $n = 14$ ) (Organon). The epinephrine and saline were added at the time of injection and the investigator was unaware of which was being used. Patients were assigned to either the epinephrine or saline group on a random basis. All anesthetics were administered by the investigator. Patients were then placed supine with approximately a 30° head-up position. Blood pressure was monitored at 1-min intervals with a Dinamap (Critikon) automatic blood pressure cuff. Any significant ( $>10\%$  systolic) decrease in blood pressure

Table 1. Patient Characteristics<sup>a</sup>

	Lidocaine (n = 15)	Lidocaine plus epinephrine (n = 14)
Age (yr)	25 ± 1.1 (range 19-33)	24 ± 1.6 (range 17-37)
Height (cm)	163 ± 1.5 (range 150-170)	165 ± 1.5 (range 158-173)

<sup>a</sup>Mean ± SEM.

was promptly treated with small (6-10 mg) doses of ephedrine intravenously. Spread and duration of sensory loss were assessed as previously described by determining loss of pinprick sensation (analgesia) (1,2,4) using a 21-gauge needle on the trunk approximately 7.5-10 cm lateral to the midline on the left. Assessment was made every 5 min until maximal sensory loss was obtained, and it was continued thereafter every 5 min until the level of anesthesia had regressed two dermatome levels. Maximal level and time to two-dermatome regression as measured by pinprick were confirmed by testing for temperature discrimination with alcohol-soaked sponges.

All data are presented as mean ± the standard errors of the mean (SEM). Ranges are also presented. Data were compared using Student's *t*-test and were considered statistically significant at *P* < 0.05.

## Results

The mean age and height of the two groups were not significantly different. Ranges were also similar (Table 1). There were no patients with clinically evident vascular disease such as atherosclerosis, preeclampsia, or essential hypertension. No patient sustained significant hypotension.

There was no significant difference between mean maximal levels of anesthesia, mean time to maximal levels, or mean time to two-level regression of the level of anesthesia. Time to two-level regression was 40 min in patients given lidocaine alone and 43 min in patients given lidocaine with epinephrine (Table 2). Correlation coefficients for maximal height vs time to two-level regression were -0.28 for the lidocaine alone group and -0.05 for the lidocaine-plus-epinephrine group.

## Discussion

The addition of epinephrine, 0.2 mg, affected neither the height nor the duration of sensory blockade in this group of young obstetrical patients. Several factors other than addition of vasoconstrictors may affect duration of spinal anesthesia. One of these is age.

Table 2. Sensory Anesthesia: Maximal Level, Time to Maximal Level, and Time to Two-Level Regression<sup>a</sup>

	Lidocaine (n = 15)	Lidocaine plus epinephrine (n = 14)
Maximal thoracic dermatomal level	6.2 ± 0.75 (range 2-10)	5.7 ± 0.70 (range 3-10)
Time to maximal level (min)	12.6 ± 1.5 (range 5-23)	13.6 ± 1.4 (range 5-23)
Time to two-level regression (min)	40 ± 3.3 (range 24-68)	43 ± 2.9 (range 36-65)

<sup>a</sup>Mean ± SEM.

Not only were the patients all young, but the two groups were comparable in age.

It is unclear why epinephrine did not alter duration of anesthesia in this group of patients. Based on our accepted model of termination of action of local anesthesia in the subarachnoid space by vascular absorption it would seem that it should. Perhaps our model is in error. Denson and others (6) have studied the pharmacokinetics of lidocaine absorption from the subarachnoid space with and without epinephrine in the rhesus monkey. They found no difference in times to peak plasma levels or in peak plasma concentrations of lidocaine with or without epinephrine. Similar data have been reported by Ravindran et al. in dogs (7). This indicates that either the vessels in the subarachnoid space (primarily pia mater) and spinal cord do not respond to epinephrine by vasoconstriction, or that lidocaine gains access to the blood by some other route. It has been shown that peak plasma levels for lidocaine are similar and are reached at about the same time after subarachnoid and epidural injection (8). This implies that a significant amount of intrathecally administered lidocaine enters the blood via the epidural veins after diffusion across the dura. If one assumes that the epidural vessels have not been affected to a significant degree by the intrathecal epinephrine, then it is not surprising that lidocaine plasma levels are not significantly affected when epinephrine is added intrathecally. It seems that if the mechanism for prolongation of spinal blockade is reduced via local anesthetic uptake (as it is in local anesthetics administered at other sites), this mechanism may not be operative in the case of subarachnoid lidocaine.

One criticism of the present study might be the possibility of "high thin blocks" because 40 mg of lidocaine produced sensory levels to T4 in several patients. These levels of anesthesia might tend to wear off more rapidly as the concentration of local anes-



thetic decreased below that necessary to maintain sensory block.

In fact, as Greene points out in his recent review (9), all such studies should be done using the same dose of the same drug to the same level. I found it very difficult to control the level of anesthesia obtained, and the range of levels obtained is similar to those in previous studies. This points out one of the difficulties in studying the effects of different variables on spinal anesthesia. However, the two groups in this study were similar in mean maximal levels and range of anesthesia. Furthermore, there was little negative correlation between maximal level and duration of block.

It is important that the efficacy of epinephrine to prolong spinal block with lidocaine be determined. Nearly every commercially prepared lidocaine spinal tray contains a 1-ml ampule of 1:1000 epinephrine. Because this should not be needed for resuscitation, one assumes it is included for use in the subarachnoid space. Its presence in the trays makes several errors possible: 1) increased risk of contamination during handling of an additional ampule and drug; 2) the chance of injecting the wrong drug during the administration of spinal anesthesia (there are reports of spinal anesthetics performed using epinephrine only [personal communication]); and 3) injection of epinephrine rather than ephedrine intravenously or intramuscularly for treatment of hypotension. It should be noted that one major company has made the two ampules, epinephrine and ephedrine, almost identical in color and lettering. Although these accidents should never occur with careful technique, anesthesiologists are often called upon to administer spinal anesthetics rapidly in urgent situations, and errors do occur. It is our goal to make the anesthetic as safe for the patient as possible. Keeping an ineffective drug in the spinal tray is unwise and costly.

In summary, the results of this study indicate that epinephrine, 0.2 mg, does not prolong the duration of spinal anesthesia performed with lidocaine in young, healthy patients. Our current concepts of local anesthetic uptake and termination of action in spinal anesthesia do not seem to explain this. Further studies of local anesthetic uptake from the subarachnoid space and termination of local anesthetic action during spinal anesthesia are warranted.

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## Atracurium Infusion Requirements in Children during Halothane, Isoflurane, and Narcotic Anesthesia

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BRANDOM BW, COOK DR, WOELFEL SK, RUDD GD, FEHR B, LINEBERRY CG. Atracurium infusion requirements in children during halothane, isoflurane, and narcotic anesthesia. *Anesth Analg* 1985;64:471-6.

*We were interested in determining the dose-response relationship of atracurium in children (2-10 yr) during nitrous oxide-isoflurane anesthesia (1%) and the atracurium infusion rate required to maintain about 95% neuromuscular blockade during nitrous oxide-halothane (0.8%), nitrous oxide-isoflurane (1%), or nitrous oxide-narcotic anesthesia. Neuromuscular blockade was monitored by recording the electromyographic activity of the adductor pollicis muscle resulting from supramaximal stimulation at the ulnar nerve at 2 Hz for 2 sec at 10-sec intervals. To estimate dose-response relationships, three groups of five children received 80, 100, 150  $\mu\text{g/kg}$  atracurium, respectively. Dur-*

*ing isoflurane anesthesia, the neuromuscular block produced by 80  $\mu\text{g/kg}$  was  $23.6\% \pm 6.5$  (mean  $\pm$  SEM), by 100  $\mu\text{g/kg}$  was  $45\% \pm 7.2$ , and by 150  $\mu\text{g/kg}$  was  $64\% \pm 8.7$ . The  $\text{ED}_{50}$  and  $\text{ED}_{95}$  (estimated from linear regression plots of log dose vs probit of effect) were 120  $\mu\text{g/kg}$  and 280  $\mu\text{g/kg}$ , respectively. At equipotent concentrations, halothane and isoflurane augment atracurium neuromuscular block to the same extent, compared to narcotic anesthesia. Atracurium steady-state infusion requirements averaged  $6.3 \pm 0.6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  during halothane or isoflurane anesthesia; the requirements during balanced anesthesia were  $9.3 \pm 0.8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  ( $P < 0.05$ ). There was no evidence of cumulation during prolonged atracurium infusion.*

Key Words: NEUROMUSCULAR RELAXANTS—atracurium. ANESTHESIA—pediatric.

Atracurium, a nondepolarizing neuromuscular blocking agent of intermediate duration of action, is noncumulative and devoid of cardiovascular effects in infants, children, and adults (1-4). Atracurium spontaneously decomposes (at physiologic pH and temperature) by Hofmann elimination and is metabolized by nonspecific esterases (2). Each pathway plays a major role in atracurium degradation (5-7). In general, the degradation of atracurium is independent of renal or liver function (8-10).

Because of its intermediate duration of action and noncumulative effects atracurium should be useful as a continuous infusion. Indeed, atracurium has been used as an infusion in adults during nitrous oxide-narcotic anesthesia (3). There are, however, age-related differences in dose requirements (i.e.,  $\text{ED}_{95}$ ) and duration of action of atracurium among infants,

children, and adults (1,2,4). These differences might influence infusion rate requirements as well. In addition, potent inhalation anesthetics may increase the neuromuscular blocking effects of atracurium and, hence, decrease infusion requirements. We were interested in determining the infusion rate of atracurium required to maintain a near steady state of neuromuscular blockade in children during nitrous oxide-narcotic, nitrous oxide-halothane, and nitrous oxide-isoflurane anesthesia.

### Patients and Methods

Seventy-five children (ASA status I-II) between 2 and 10 yr old, having low to moderate risk elective surgical procedures requiring endotracheal intubation were studied. No patient received aminoglycoside antibiotics or antihistamines within 48 hr of the study. The study was approved by the Human Rights Committee of the Children's Hospital of Pittsburgh. Informed consent was obtained from a parent. Most patients received some combination of secobarbital (1 mg/kg), morphine (0.1-0.15 mg/kg), and scopolamine (0.01 mg/kg) intramuscularly 1 hr before induction of anesthesia. The study was divided into two parts.

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### Part I

The dose-response curve for atracurium during nitrous oxide-oxygen-isoflurane (1% end-tidal) anesthesia was determined in 15 children as previously described (1). After induction of general anesthesia, the ulnar nerve was stimulated supramaximally with repetitive trains-of-four (2 Hz for 2 sec at 10-sec intervals) at the wrist with surface electrodes. The evoked compound electromyogram of thumb adduction was amplified, analog to digital converted, reconstructed, and recorded by a prototype microprocessor. Three subgroups of five children received an initial bolus of atracurium selected to approximate the ED<sub>25</sub>, ED<sub>50</sub>, and ED<sub>75</sub> (i.e., 80, 100, and 150  $\mu\text{g/kg}$ ). These doses were selected because we assumed that the dose-response curve for atracurium during isoflurane anesthesia would be shifted to the left, but would be parallel to that curve for halothane anesthesia. The degree of neuromuscular block was described as percent of control in that the height of the first train-of-four response was compared with the control EMG height.

The maximum percent neuromuscular block from these single doses of atracurium was transformed to probit values. Composite linear dose-response curves using both  $\mu\text{g/kg}$  and  $\mu\text{g/m}^2$  as dose units were determined by log-probit transformation of the data and calculation by the method of least squares (11). The surface area of each child was estimated from standard nomograms of height and weight (12). Estimates of the ED<sub>95</sub> and ED<sub>50</sub> of atracurium were made from the regression equations. The slope and intercept of the regression line for atracurium dose-effect during isoflurane anesthesia were compared to that determined previously during halothane and balanced anesthesia using analysis of covariance (1,13). The time required for neuromuscular transmission to return to 25% of control ( $T_{25}$ ), to 50% ( $T_{50}$ ), to 75% ( $T_{75}$ ), and to 95% ( $T_{95}$ ) after the last injection of atracurium was noted for those children who achieved a block between 92 and 97% (mean  $95 \pm 0.8\%$  SEM) from either single or cumulative doses of atracurium. The T4:T1 ratios were calculated at these points in recovery of neuromuscular function.

### Part II

In a pilot study, thirty children were assigned randomly to one of three study groups. Ten patients received nitrous oxide-oxygen-halothane (group A); ten patients received nitrous oxide-oxygen-isoflurane (group B); and ten patients received nitrous oxide-thiopental-fentanyl (group C). In patients in group A and group B, anesthesia was induced with

nitrous oxide-oxygen and the potent anesthetic, then a venous catheter was inserted. The inspired and end-tidal concentrations of halothane and isoflurane were monitored continuously with a Perkin-Elmer mass spectrometer. Anesthesia was maintained with 70% nitrous oxide with halothane (0.8% end-tidal) in oxygen or with isoflurane (1.0% end-tidal) in oxygen. End-tidal concentrations of anesthetic were allowed to stabilize prior to administration of atracurium. In patients in group C, anesthesia was induced with 70% nitrous oxide-oxygen and thiopental (4 mg/kg) intravenously and maintained with 70% nitrous oxide-oxygen and fentanyl (2-4  $\mu\text{g/kg}$ ).

After induction of general anesthesia, neuromuscular transmission was monitored as described in part I. A dose of atracurium approximately equal to the ED<sub>95</sub> for the given anesthetic (determined from this and previous studies) (1) was administered as a bolus. To facilitate patient dosing, the ED<sub>95</sub> of atracurium was taken as 300  $\mu\text{g/kg}$  for balanced anesthesia and 250  $\mu\text{g/kg}$  for halothane and isoflurane anesthesia. The maximum neuromuscular blocking effect was recorded, and the trachea was intubated. When neuromuscular blockade had stabilized between 89 and 99% or when neuromuscular transmission had returned, a continuous infusion of atracurium (200  $\mu\text{g/ml}$  in 5% dextrose/water) was administered with a continuously variable infusion pump. Variable infusion rates were set for 15-min periods and the change in neuromuscular blockade, if any, was noted for this time period. Projections from these data suggested that an infusion rate of 5-6  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  would be required to maintain 95% neuromuscular blockade during nitrous oxide-halothane or nitrous oxide-isoflurane anesthesia, and that 9-10  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  would be required during nitrous oxide-narcotic anesthesia. These estimated infusion rates were used as starting points for the definitive part of the study.

An additional 30 children were again randomly assigned to one of three anesthetic study groups. Atracurium ( $1 \times \text{ED}_{95}$ ) was administered and neuromuscular blockade was monitored. When neuromuscular blockade had stabilized between 89 and 99% block or when neuromuscular transmission began to recover, an infusion of atracurium was begun at the rate predicted for that anesthetic from the pilot study. The infusion rate was adjusted to maintain neuromuscular block within the range of 89-99%. The atracurium infusion was continued for as long as required by the surgical procedure (range 15-228 min) to provide surgical relaxation. For each patient the infusion rate of atracurium required to achieve this goal (89-99% blockade) was calculated and recorded for each 3-min period. These data were collated into 9-min epochs

by calculating the mean for three consecutive 3-minute time periods. Data from 3-minute periods during which neuromuscular block was outside the 89–99% range were not included in analyses. For each patient the mean of all 9-min qualifying epochs was determined. Within anesthetic groups the individual patient means were then averaged to obtain a group mean. No weighting based on the number of epochs per patient was used. Atracurium infusion requirements were calculated on both a  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  and  $\mu\text{g}\cdot\text{m}^{-2}\cdot\text{min}^{-1}$  basis.

Standard errors are shown for all mean values. An analysis of variance (ANOVA) followed by a multiple range test (Student–Newman–Keuls, SNK) was used to assess differences between groups (13). A multiple linear regression analysis was used where appropriate. Statistical differences were considered significant at  $P < 0.05$ .

## Results

During isoflurane anesthesia in children, the neuromuscular blockade achieved with atracurium ( $80\ \mu\text{g}/\text{kg}$ ) was  $23\% \pm 6.5$  (mean  $\pm$  SEM), with  $100\ \mu\text{g}/\text{kg}$  was  $45\% \pm 7.2$ , and with  $150\ \mu\text{g}/\text{kg}$  was  $64\% \pm 8.7$ . Calculated dose–response values are presented in Table 1. The log dose ( $\mu\text{g}/\text{kg}$ ) probit regression line for atracurium (intravenous bolus) determined during isoflurane anesthesia in part I of this study is shown in Figure 1 along with atracurium dose–response curves previously determined during halothane and thiopental–fentanyl (balanced) anesthesia (1). The dose–response curves for the three groups are parallel. The dose–response curve for patients receiving isoflurane is shifted significantly to the left of the curve for balanced anesthesia (i.e., the intercepts are different). There was no difference between the position (intercept) of the line for patients receiving halothane or isoflurane. After one or more injections of atracurium that produced  $95 \pm 0.9\%$  neuromuscular blockade, neuromuscular transmission spontaneously returned to  $T_{25}$  in  $14.6 \pm 1.0$  min ( $n = 10$ ), to  $T_{50}$  in  $20.5 \pm 1.2$  min ( $n = 7$ ), to  $T_{75}$  in  $24.0 \pm 2.3$  min ( $n = 6$ ), and to  $T_{95}$  in  $29.6 \pm 2.2$  min ( $n = 5$ ). The  $T_4:T_1$  ratio at  $T_{25}$  was  $0.27 \pm 0.03$ , at  $T_{50}$  was  $0.44 \pm 0.04$ , and at  $T_{75}$  was  $0.65 \pm 0.05$ .

Early in the course of a patient's infusion, rate adjustments were needed often to obtain the optimal infusion rate. The amount of atracurium required to maintain stable neuromuscular blockade became less variable after this period (Fig. 2). There was no evidence of cumulation over the duration of the infusion as assessed by a repeated measures ANOVA on the mean infusion rate for the 3-min periods in the 9-min

Table 1. Mean  $\text{ED}_{50}$  and  $\text{ED}_{95}$  Values for Atracurium in Anesthetized Children

Anesthetic	$\text{ED}_{50}$ ( $\mu\text{g}/\text{kg}$ )	$\text{ED}_{95}$ ( $\mu\text{g}/\text{kg}$ )	$\text{ED}_{50}$ ( $\mu\text{g}/\text{m}^2$ )	$\text{ED}_{95}$ ( $\mu\text{g}/\text{m}^2$ )
Thiopental–fentanyl	170	350	3900	8200
Halothane	130	260	3300	6600
Isoflurane	120	280	3000	8600

epoch (i.e., the mean infusion rate for 9-min epochs early in the infusion was similar to that at the end of the infusion period). When the data were analyzed by means of multiple linear regression, neither the time from bolus injection nor the time since the infusion was initiated were significant factors in predicting the effect of a given atracurium infusion rate. Mean infusion rate requirements during the various anesthetics in the definitive portion of part II are listed in Table 2. Atracurium infusion rate requirements were higher during nitrous oxide–narcotic anesthesia on either a  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  or  $\mu\text{g}\cdot\text{m}^{-2}\cdot\text{min}^{-1}$  basis than for the potent inhalation anesthetics ( $P < 0.05$ , ANOVA, SNK). There was no difference between the atracurium infusion rate requirements between the two potent anesthetics.

After termination of the infusion, the time interval for neuromuscular transmission to spontaneously recover to  $T_{25}$  was  $7.9 \pm 0.6$  min ( $n = 15$ ); the time to  $T_{95}$  was  $20.9 \pm 0.7$  min ( $n = 8$ ). In six patients, neostigmine ( $0.07\ \text{mg}/\text{kg}$ ) was given with atropine ( $0.03\ \text{mg}/\text{kg}$ ) and recovery was monitored to  $T_{95}$ . Although neuromuscular transmission in these six patients varied between  $T_{10}$  and  $T_{90}$  when neostigmine was given, recovery to  $T_{95}$  was never longer than 6 min and averaged  $2.5 \pm 0.8$  min.

## Discussion

In previous studies we demonstrated age-related differences in atracurium dose requirements and duration of action between infants, children, and adults (1,4). On a weight basis ( $\mu\text{g}/\text{kg}$ ) the  $\text{ED}_{50}$  and  $\text{ED}_{95}$  for atracurium are similar in infants and adolescents; children 2–10 yr old had higher dose requirements. If dose is calculated on a surface area basis (a procedure that partly corrects for marked differences in the apparent volume of distribution of relaxants in patients of disparate age and size), the dose–response curves for children and adolescents are identical; the dose–response curve for infants is shifted to the left.

This study in children was designed to determine the  $\text{ED}_{50}$  and  $\text{ED}_{95}$  of atracurium during nitrous oxide–isoflurane anesthesia and to examine the influence of potent anesthetics on atracurium infusion re-



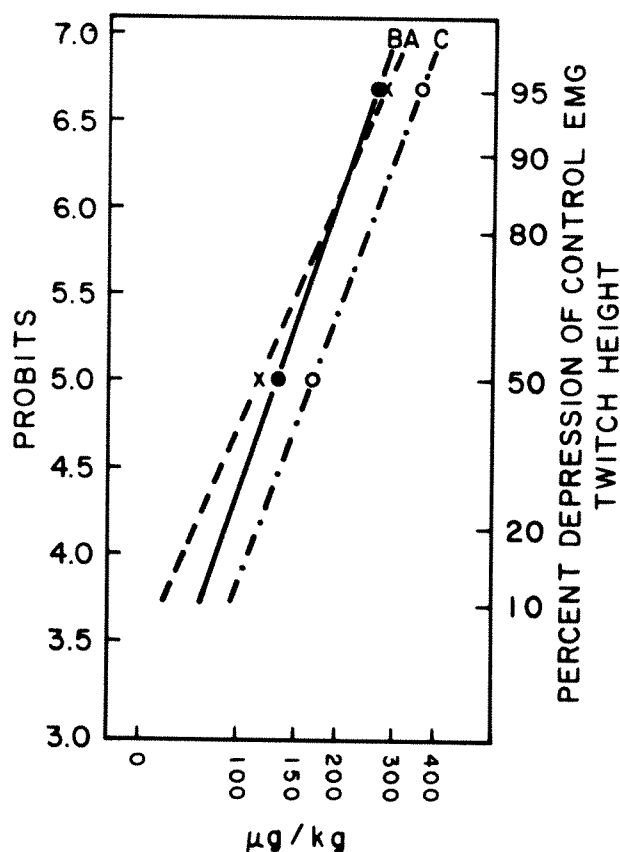


Figure 1. Mean dose-response curves for atracurium ( $\mu\text{g/kg}$ ) for children during isoflurane (A), halothane (B), or balanced (C) anesthesia. Data for halothane and balanced anesthesia are from (1).

quirements. The addition of isoflurane to nitrous oxide significantly decreased the  $\text{ED}_{50}$  of atracurium by about 30%, compared with the  $\text{ED}_{50}$  determined during nitrous oxide-narcotic anesthesia. At equipotent concentrations there was no difference between the intravenous bolus dose requirements of atracurium during nitrous oxide-halothane or nitrous oxide-isoflurane anesthesia. Likewise, isoflurane and halothane at the concentrations used, equally reduced atracurium infusion requirements, compared to nitrous oxide-narcotic anesthesia.

Potent inhalation anesthetics are known to augment long-acting nondepolarizing relaxants in a dose-(concentration)-related manner (14). The augmentation is more marked with enflurane or isoflurane than with halothane (15-17).

Intermediate-acting relaxants may not be augmented by potent anesthetics in the same manner. For example, at 0.6 MAC concentrations, Rupp et al. (18) noted that the augmentation of neuromuscular blockade of vecuronium by isoflurane and halothane appears similar; at 1.6 MAC concentrations, isoflurane augmented the vecuronium neuromuscular

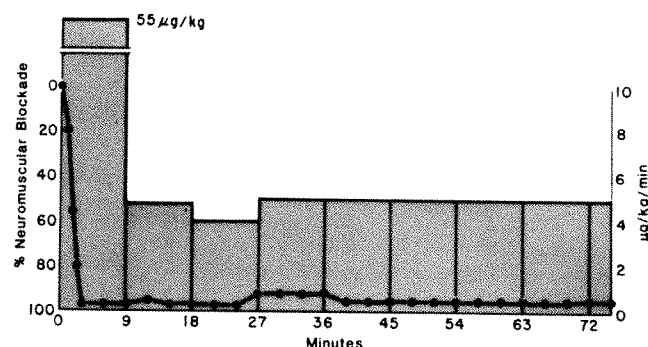


Figure 2. Evolution of atracurium requirements calculated for 9-min epochs (shaded area) to maintain neuromuscular blockade (solid dots) in a typical patient. The first epoch represents in large part the bolus injection.

blockade to a greater extent than did halothane. More importantly, increasing the concentration of the potent anesthetic produced little additional augmentation of the neuromuscular blockade from vecuronium. In our studies, the end-tidal concentration of the potent anesthetics was kept constant. Therefore, the relationship between atracurium requirements as a bolus or as an infusion during various depths of anesthesia is unclear.

In order to more quickly achieve a near steady-state plasma concentration of atracurium and hence a uniform degree of neuromuscular blockade, we combined a bolus and infusion of atracurium (19-21). In general, the initial amount of atracurium required to produce and maintain a given degree of paralysis depends upon both distribution to various tissue depots and removal. Later, removal becomes the sole determinant of the amount of atracurium required. To maintain a steady-state plasma concentration of atracurium, the infusion rate must counterbalance the rate of atracurium removal (i.e., the infusion rate equals the rate of removal). Removal can be related to plasma clearance ( $\text{Clp}$ ) and plasma steady-state concentration ( $\text{Css}$ ) by the following equation:

$$R = \text{Clp} \times \text{Css}. \quad (1)$$

Plasma clearance is defined as the volume of plasma from which drug is completely removed in unit time. Plasma clearance is a function of both the elimination half-life ( $t_{1/2B}$ ) and the volume of drug distribution ( $Vd$ ):

$$\text{Clp} = 0.693 Vd/t_{1/2B}. \quad (2)$$

Thus differences in clearance may be a reflection of differences in the distribution volume, the elimination half-life of the drug, or both. Atracurium distribution, spontaneous degradation, metabolism, and elimination through the liver or kidney determine clearance.

Table 2. Atracurium Infusion Requirements for Surgical Relaxation during Various Anesthetics in Children

Anesthetic	Infusion Rate <sup>a</sup> ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	Infusion Rate <sup>a</sup> ( $\mu\text{g}\cdot\text{m}^{-2}\cdot\text{min}^{-1}$ )
Thiopental-fentanyl	$9.3 \pm 0.8$ (6.6–13.6)	$226 \pm 15$ (171–309)
Halothane	$6.8 \pm 0.5$ (4.8–9.3)	$175 \pm 19$ (104–274)
Isoflurane	$5.9 \pm 0.7$ (4.4–9.3)	$147 \pm 16$ (94–217)

<sup>a</sup>Mean  $\pm$  SEM (range). Different from thiopental-fentanyl  $P < 0.05$ , ANOVA, SNK.

Our study was not designed specifically to examine the pharmacokinetics of atracurium. However, we have determined that the clearance of atracurium is  $5.1 (\pm 0.2 \text{ SEM}) \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in children anesthetized with isoflurane (10). If clearance were considered a constant independent of anesthetic technique, the steady-state plasma concentration of atracurium associated with 89–99% neuromuscular blockade (estimated from equation (1)) would be several-fold higher during so-called balanced anesthesia than with halothane or isoflurane anesthesia. These data agree with our other evidence that halothane and isoflurane potentiate neuromuscular blockade to the same degree. This concept can be confirmed with pharmacodynamic studies.

The atracurium infusion requirements in children during nitrous oxide-narcotic anesthesia can be compared to those noted in several age-groups of adults during similar anesthesia. D'Hollander et al. (3) noted that in patients 16–85 yr old, the steady-state atracurium infusion rate averaged  $14.4 \text{ mg}\cdot\text{m}^{-2}\cdot\text{hr}^{-1}$ ; this corresponds to  $240 \mu\text{g}\cdot\text{m}^{-2}\cdot\text{min}^{-1}$ . This value is similar to the rate we noted of  $226 \mu\text{g}\cdot\text{m}^{-2}\cdot\text{min}^{-1}$ . In both studies there was a considerable range in the required infusion rate and, hence, removal. When infusion requirements are expressed on a surface area basis, the rate of removal of atracurium appears independent of age from 2 to 85 yr. In contrast, vecuronium requirements decrease in infants and with advancing age (22). Vecuronium is excreted largely unchanged via the hepatobiliary system (40–50%) or through the kidneys (4–14%); some biotransformation takes place in the liver (23). These processes may be affected by physiologic changes at the extremes of age or by significant liver or renal disease. On the other hand, atracurium is metabolized by plasma esterases and is degraded by Hofmann elimination—both processes that appear to be independent of liver or renal function.

From a clinical standpoint, this study demonstrates that equipotent concentrations of halothane and isoflurane equally reduce atracurium infusion requirements in children, compared to those determined during nitrous oxide-narcotic anesthesia. After a bolus

of atracurium that will produce about 95% neuromuscular blockade,  $9\text{--}10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  of atracurium is a useful initial infusion rate in children under balanced anesthesia, whereas  $5\text{--}6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  is a useful initial rate in children anesthetized with halothane or isoflurane in addition to nitrous oxide. The mean infusion rate required for each anesthetic background can only serve as a starting point for the infusion of atracurium because there was a wide range in steady-state infusion rate requirements in these patients. Obviously, neuromuscular blockade must be monitored to titrate the effect of atracurium when it is given as an infusion. No cumulation of atracurium occurs during prolonged infusion. At the termination of the infusion, spontaneous recovery of neuromuscular transmission occurs rapidly; alternatively, reversal of blockade is easily achieved with neostigmine.

We are particularly indebted to Dr. Robert Hirsch, Biostatistician in the Department of Community Medicine, for his advice on statistics and data management. In addition, Dr. Lemuel B. Wingard, Professor of Pharmacology and Anesthesiology, provided valuable insight about the pharmacokinetic issues of this infusion study.

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## Acid and Alkaline Solutions of Local Anesthetics: Duration of Nerve Block and Tissue pH

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BUCKLEY FP, NETO GD, FINK BR. Acid and alkaline solutions of local anesthetics: duration of nerve block and tissue pH. *Anesth Analg* 1985;64:477-82.

*The effect of solution pH on the duration of rat infraorbital nerve blocks produced by 1% lidocaine or 0.25% bupivacaine at pH 5.0 and 7.4, with and without epinephrine was investigated in a double-blind study. The time course of tissue pH changes subsequent to injections into the infraorbital*

*area or abdominal musculature of rats was measured with a tissue pH microelectrode. Injectate pH had little or no effect upon the duration of block. Tissue pH was minimally changed by the injection of solutions at pH 7.4, but decreased appreciably with injections of solutions at pH 5.0, or if the injectate contained epinephrine.*

Key Words: ANESTHETICS, LOCAL—pH effects.

Alkaline solutions of local anesthetics have been reported to produce a more rapid onset of anesthesia and to be more potent in vitro (i.e., greater degree of block with a given concentration) than acidic solutions (1-5) and, in animal studies using complex solutions to buffer local anesthetic (6) and with non-epinephrine-containing solutions in humans (7), to have a longer duration of action. We wished to investigate the possible prolongation of local anesthetic block beyond the longest durations seen in clinical practice (i.e., with epinephrine-containing solutions) using buffered local anesthetics. The rat infraorbital nerve (8) is amenable to observer-blinded measurement of duration of local anesthetic block and was used in this study to investigate the correlation of duration of block with pH of local anesthetic and with changes in tissue pH.

### Methods

Commercial solutions of local anesthetics without preservative, lidocaine 1% (Astra) (pKa 7.9) (9) or bupivacaine 0.25% (Breon) (pKa 8.1) (9), were titrated to pH 5.0 with 0.1N hydrochloric acid or to pH 7.4 with 0.2N sodium hydroxide. Solution pH was measured using a pH probe (Radiometer pH meter M63 and standard Corning Buffer, pH 7.0, Corning Glass

Works, Corning, NY). Commercially supplied epinephrine 1:200,000 was added to some solutions immediately prior to pH adjustment and measurement. Male Tyler rats weighing 500-600 g each were sedated with intraperitoneal sodium pentobarbital (18-20 mg) as previously described (10) and were secured in a holding frame.

### Group I

In 85 rats (Table 1) bipolar stimulating needle electrodes were placed in both upper lips in the areas supplied by the infraorbital nerve. Bipolar electromyogram (EMG) recording electrodes were placed percutaneously into the pretracheal musculature. Aversive stimuli of square-wave pulses of 10 V, 1-msec duration, were delivered to both lips from a stimulation unit (WPI stimulator 381, WPI stimulus isolator). The compound EMG of the pretracheal muscle twitch that occurred in response to the aversive stimuli was recorded on an oscilloscope (Tektronix 532, Tektronix Limited, Beaverton, OR) and was photographed (Fig. 1).

Left infraorbital nerves in group I rats were injected with coded solutions (see Table 1) using a specially constructed, previously described jig (8). In group I the code was broken after the completion of all experiments in this group. All injections were performed by one investigator (GDN).

Immediately after injection, both upper lips of the animals were stimulated at 10-sec intervals for 2 min. Block was considered successful when the pretracheal EMG, on the blocked (left) side, was obliterated within

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Table 1. Duration  $\pm$  SD (min) of Infraorbital Nerve Block of Animals in Group I

Drug	Group	(n)	Volume (ml)	Duration $\pm$ SD (min) of nerve block			
				pH 5.0	(n)	pH 7.4	(n)
Lidocaine 1%	IA	(16)	0.2	111 $\pm$ 48	(8)	93 $\pm$ 22	(8)
	IB	(14)	0.2 + epi	145 $\pm$ 40	(7)	135 $\pm$ 40	(7)
	IC	(16)	0.4 + epi	153 $\pm$ 34	(8)	177 $\pm$ 39	(8)
Bupivacaine 0.25%	ID	(12)	0.2 + epi	146 $\pm$ 15	(6)	160 $\pm$ 35	(6)
	IE	(27)	0.4 + epi	169 $\pm$ 22	(14) <sup>a</sup>	198 $\pm$ 19	(13)

Abbreviations: epi, epinephrine 1:200,000.

<sup>a</sup>Significant intergroup difference,  $P < 0.05$ 

2 min (Fig. 1(B)). Animals that did not satisfy this criterion were excluded from the study. Onset of block was so rapid that comparisons of the speed of onset of block were impractical. Thereafter the blocked side and control (right) side were stimulated at 5-min intervals. The time from injection to onset of EMG recovery was taken as the duration of the nerve block (Fig. 1(D),(E)). Any animal that failed to respond to stimulation on the unblocked (right) side at any time during an experiment was excluded from the report.

### Group II

Tissue pH (pHt) was measured with a microelectrode (Microelectrode MI 408, Microelectrodes Inc., Londonderry, NH); response time was 2 min. In 24 animals (Fig. 2) the microelectrode was positioned at the left infraorbital foramen from inside the mouth, the reference electrode being placed subcutaneously in the chest. Stimulating and recording electrodes were placed as in group I, and the left infraorbital nerve was injected with 0.4 ml of 1% lidocaine (uncoded) at pH 5.0 and 7.4, with and without epinephrine 1:200,000 (each solution, six animals). The protocol for evaluating onset and duration of nerve block was the same as in group I. Tissue pH was monitored for 3 hr after injection.

### Group III

Because the distance from the point of infraorbital injection to the recording surface of the pHt electrode was somewhat indeterminate, experiments were performed in a further group of 42 animals (Figs. 3, 4) in which the distance between the pHt electrode and the site of injection was standardized. With the pHt probe placed in the abdominal musculature, a 30-g needle was introduced percutaneously to exactly 1 mm beyond the tip of the pHt microelectrode, at which point 0.4 ml of uncoded solution was injected. The solutions were 0.9% saline at pH 5.0 or 7.4, or 1%

lidocaine with or without epinephrine 1:200,000 at pH 5.0 or 7.4 (each group comprised six animals). Tissue pH was monitored for 3 hr after injection. Statistical analysis was by Student's *t*-test, paired or unpaired as appropriate,  $P < 0.05$  being considered statistically significant.

## Results

### Observer-Blind Study of Duration of Block (Group I, Table 1)

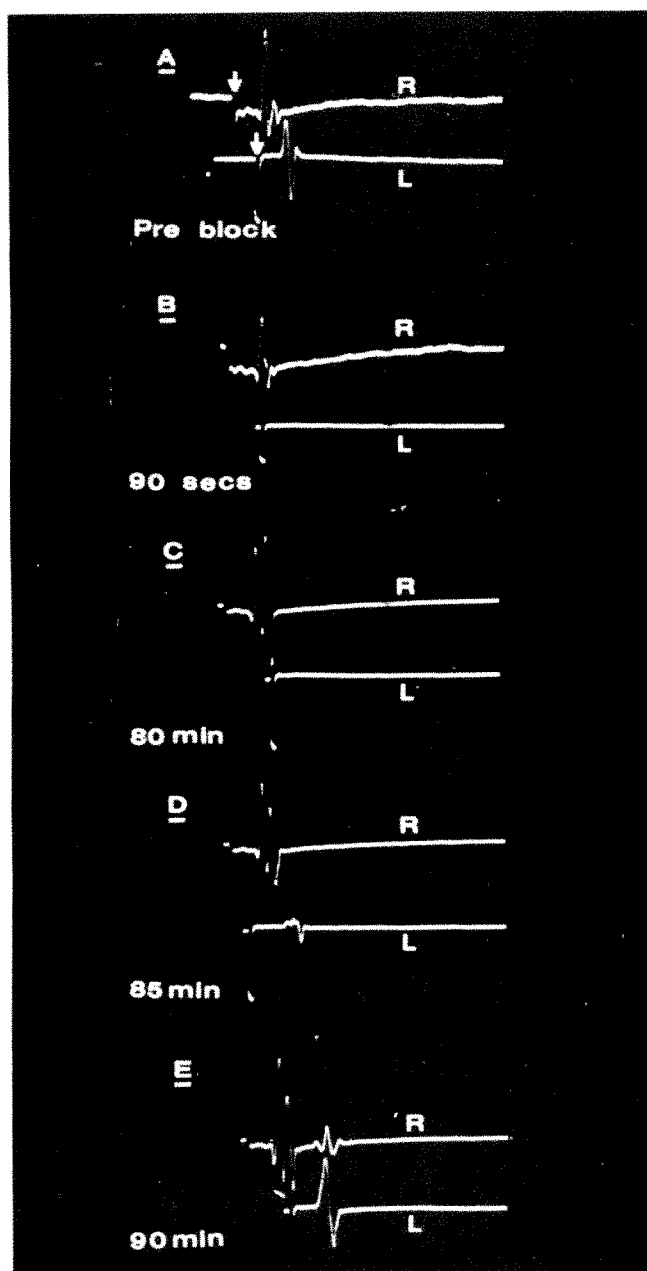
When a low volume (0.2 ml) of injectate was used (Table 1, groups IA, IB, and ID), there was no significant difference in the duration of action between the solutions at the two pH values. When a larger volume (0.4 ml) (Table 1, groups IC and IE) was injected, solutions at pH 7.4 produced blocks of longer duration, but only in the case of bupivacaine was the difference statistically significant ( $P < 0.05$ ) (Table 1, group IE).

### Duration of Infraorbital Nerve Block with pHt Electrode in Site at Infraorbital Foramen

The mean duration of block produced by lidocaine 0.4 ml plus epinephrine at pH 7.4 (mean 145 min) and pH 5.0 (mean 125 min) (Group II, Fig. 2) was not significantly different from the mean duration of block produced by similar solutions at pH 7.4 (mean 177 min) and pH 5.0 (mean 150 min) when blocks were produced in the observer-blind investigation without the pHt electrode in place (Table 1, group IC). Within group II there were no significant differences in mean duration of nerve blocks produced by solutions at pH 7.4 when compared to solutions at pH 5.0.

### Tissue pH Values in the Infraorbital Region and in the Abdominal Musculature

After probe placement alone (no injections), pH was essentially stable at, and not different from, control



**Figure 1.** Oscilloscope recording of pretracheal muscle twitch EMG resulting from aversive stimuli to the right (unblocked) and left (blocked) upper lips at various times. Initial spike (marked by an arrow in A) is stimulus artifact. Duration of block in this instance 85 min. (A) Before block. (B) 90 sec after block with 1% lidocaine 0.2 ml to the left infraorbital nerve. Note the loss of EMG response to left sided stimulus. (C) 80 min after block. EMG still absent in response to left sided stimulus. (D) 85 min after block. First sign of recovery of EMG response to left stimulus. (E) 90 min after block. Continued recovery of EMG response to left stimulus.

values throughout the investigation (Fig. 3, group IIIA). Saline at pH 7.4 produced a modest decrease in pHt that was significantly different ( $P < 0.05$ ) from the pHt resulting from probe placement alone for 30–50 min (Fig. 3, group IIIA vs group IIIB). In general,

injection of epinephrine-free solutions at pH 5.0 produced significant ( $P < 0.05$ ) decreases in pHt, compared to same solutions at pH 7.4; the duration of significant differences lasting between 30 min (Fig. 3, group IIID vs group IIIE) and 90 min (Fig. 2, group IIIA vs group IIIC; Fig. 3, group IIIB vs group IIIC).

The presence of lidocaine in the injectate had a relatively minor influence on the pHt, decreases being small and of short duration when compared to 0.9% saline at either pH (Fig. 3, group IIIB vs group IIID, group IIIC vs group IIIE).

The most pronounced and prolonged effects upon pHt were seen with the addition of epinephrine to lidocaine at either pH. Significant differences ( $P < 0.05$ ) existed between epinephrine- and non-epinephrine-containing solutions for 120–180 min at pH 7.4 (Fig. 2, group IIA vs group IIB; Fig. 4, group IIID vs group IIIG) and for 150–180 min at pH 5.0 (Fig. 2, group IIC vs group IID; Fig. 4, group IIIE vs group IIIG). Epinephrine-containing solutions at pH 5.0 produced consistently greater and longer lasting (150–180 min) decreases in pHt than epinephrine-containing solutions at pH 7.4 (Fig. 2, group IIB vs group IID; Fig. 4, group IIIE vs group IIIG). The lowest mean pHt values were observed after the injection of lidocaine plus epinephrine solutions at pH 5.0, the nadir being pHt 6.4–6.5 at 20–30 min after injection (Fig. 2, group IID; Fig. 4, group IIIG).

## Discussion

We found that raising solution pH had minimal effects upon duration of local anesthetic action. Although solutions at pH 7.4 had longer durations of action than solutions at pH 5.0, in some circumstances (Table 1, group IC, group ID), the differences were not significant. The statistically significant prolongation of action (approximately 20%) seen with high volumes of bupivacaine at pH 7.4 (Table 1, group IE) is probably unimportant clinically.

Our results, consistent with the lack of effect of solution pH upon duration of action of either procaine (11) or lidocaine (12,13) reported by early workers in dental anesthesia, differ from more recent work. Studies of bupivacaine in animals (6) and of mepivacaine in epidural anesthesia in humans (7) have reported that raising solution pH prolonged duration of action by approximately 50%.

The investigations in which prolongation of local anesthetic action was observed with alkaline solutions were performed with epinephrine-free solutions (6,7). We used primarily epinephrine-containing solutions, because we were concerned with investigating any prolongation of action beyond the longest durations



Figure 2. Rat infraorbital nerve block in group II. Mean tissue pH and mean duration of block  $\pm$  SD (min) after the following injections: group IIA,  $\circ$ —lidocaine 1% pH 7.4; group IIB,  $\bullet$ —lidocaine 1% plus epinephrine 1:200,000 pH 7.4; group IIC,  $\square$ —lidocaine 1% pH 5.0; group IID,  $\blacksquare$ —lidocaine 1% plus epinephrine 1:200,000 pH 5.0. All groups  $n = 6$ . All injections 0.4 ml. Student's paired  $t$  test. \* =  $P < 0.05$ , \*\* =  $P < 0.01$ .

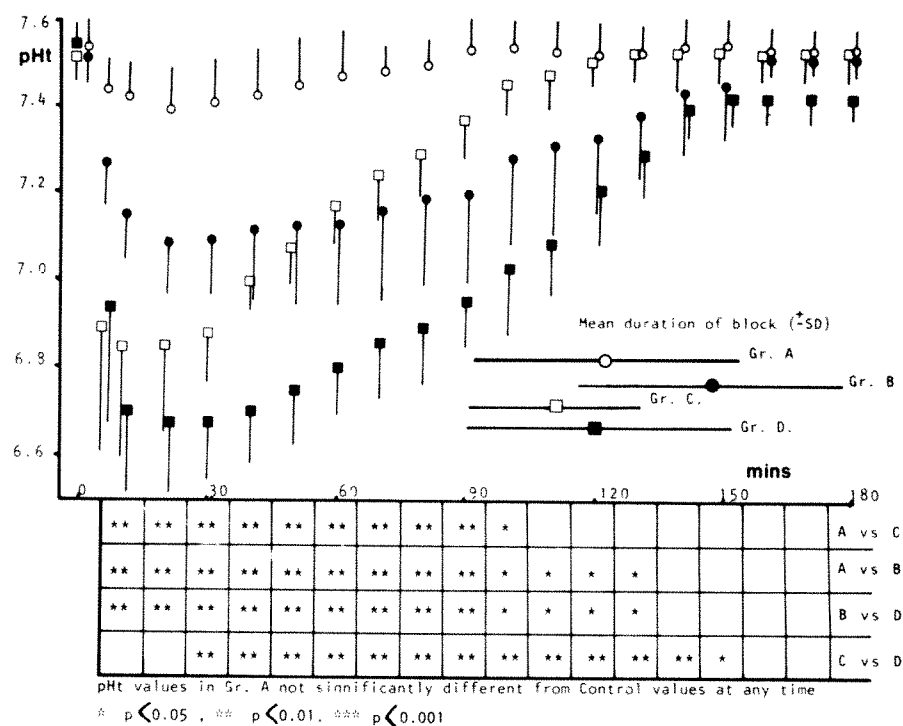
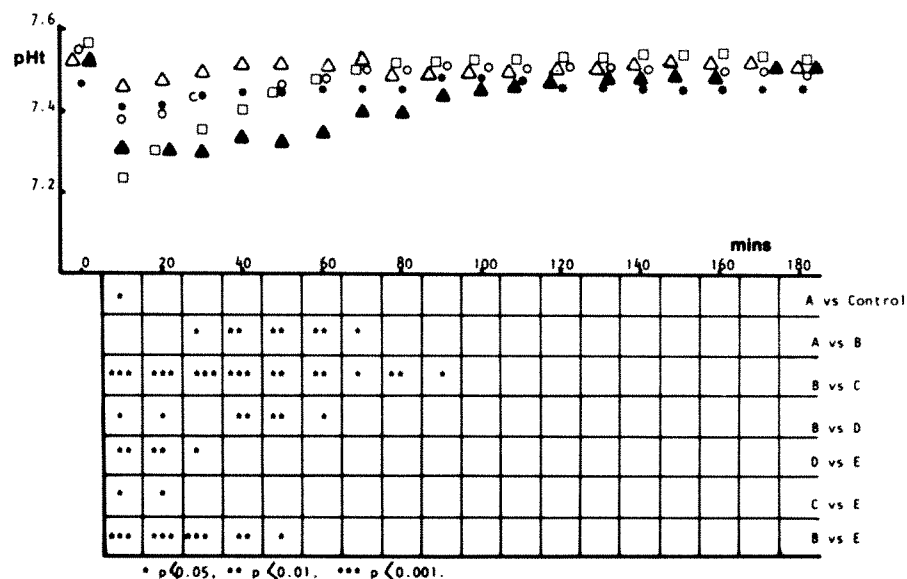


Figure 3. Group III. Rat abdominal muscle. Mean tissue pH (SD omitted for clarity) after the following injections: group IIIA, \*—probe placement alone, no injection; group IIIB,  $\triangle$ —0.9% saline pH 7.4; group IIIC,  $\blacktriangle$ —0.9% saline pH 5.0; group IIID,  $\circ$ —1% lidocaine pH 7.4; group IIIE,  $\square$ —1% lidocaine pH 5.0. All groups  $n = 6$ . All injections 0.4 ml. Student's paired  $t$ -test. \* $P < 0.05$ , \*\* =  $P < 0.01$ , \*\*\* =  $P < 0.001$ .

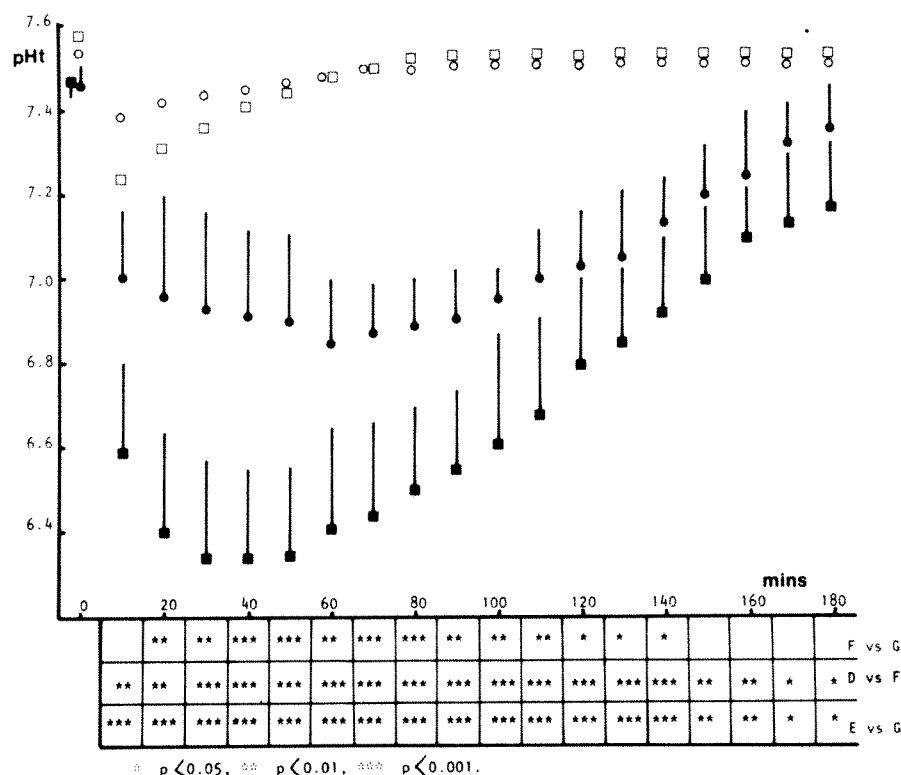


of action produced by conventional local anesthetic solutions, i.e., solutions containing epinephrine.

Both studies showing a prolongation of action with alkaline solutions were performed in a double-blind fashion, as was this study. Animal nerve blocks were performed with the aid of a nerve stimulator (6). Whether such a technique results in as equally consistent placement of drug as the present technique, or results in intraneuronal placement is not known.

Moreover the pH of the solution was higher (pH 8.0–9.0) than used in this experiment. It may not be valid to compare the results found in peripheral nerve blocks with those found in epidural anesthesia. In the former the major barrier to local anesthetic diffusion is the perineurium, whereas in the latter the drug must penetrate a number of biological membranes before reaching its potential sites of action. Differences between acid and alkaline solutions in epidural

Figure 4. Group III. Rat abdominal muscle. Mean tissue pH ( $\pm$  SD) after the following injections: group IIID,  $\circ$ —1% lidocaine pH 7.4; group IIIE,  $\square$ —1% lidocaine pH 5.0; group IIIF,  $\bullet$ —1% lidocaine plus epinephrine 1:200,000 pH 7.4; group IIIG,  $\blacksquare$ —1% lidocaine plus epinephrine 1:200,000 pH 5.0. All groups  $n = 6$ . All injections 0.4 ml. Student's paired  $t$ -test. \* $P < 0.05$ , \*\* =  $P < 0.01$ , \*\*\* =  $P < 0.001$ .



anesthesia may be a reflection of the ability of the alkaline solution to penetrate those biological membranes more effectively than the acidic solution.

The techniques used in this investigation would appear to be reliable, because the durations of actions reported are consistent with those reported previously (8,10,14) and, within this study, the mean duration of action of lidocaine with epinephrine (0.4 ml) was similar in separate parts of the investigation (Table 1, group IC; Fig. 2, group IIB, IID).

It has been reported that rapid buffering of acidic injectates (pH 6.0) occurs in the epidural space of the dog (15). If such rapid buffering occurred in this investigation it might account for the lack of difference in duration of action between the injectates. However, pHt observed at the site of injection was significantly lower after the injection of both epinephrine-free and epinephrine-containing solutions at pH 5.0 for considerable periods of time (Fig. 2, group IIA vs group IIC; group IIB vs group IID), compared to similar solutions at pH 7.4.

The pHt at the site of injection may be influenced by the presence of the pHt probe, but largely will be the result of the interaction of the buffer demand of the injectate and the buffer capacity of the tissue. The buffer capacity of tissue may be influenced by tissue blood flow, and factors which influence that, such as tissue compression by the injectate, or the presence

of vasoconstrictors in the injectate. We found that placement of the pHt probe (Fig. 3, group IIIA) and tissue compression produced by saline at pH 7.4 (Fig. 3, group IIIB) did little to influence pHt. Acidic solutions consistently produced greater and more prolonged decreases in pHt than alkaline solutions for either saline (Fig. 3, group IIIB vs group IIIC) or lidocaine (Fig. 2, group IIA vs group IIC; Fig. 3, group IIID vs group IIIE). The inclusion of lidocaine in the injectate at either pH had little effect upon pHt changes, compared to saline solutions at similar pH (Fig. 3, group IIIB vs group IIID; group IIIC vs group IIIE).

Although the addition of epinephrine to lidocaine at pH 6.5 does little to alter buffer demand in vitro (16), epinephrine-containing solutions produced profound and prolonged decreases in pHt, compared to epinephrine-free solutions in our animals (Fig. 2, group IIA vs group IIB; group IIC vs group IID; Fig. 4, group IIID vs group IIIF; group IIIE vs group IIIG).

The decreases in pHt after the injection of acidic epinephrine-free solutions observed in this study contrast the absence of change observed when similar solutions were injected into the dog epidural space (15), but are of a similar magnitude to those seen after the injection of similar solutions into the rat abdominal wall (17) or the rabbit abdominal panniculus (18). The decreases in pHt observed after the injection of epinephrine-containing solutions were similar to those



seen after the injection of epinephrine solutions into the rabbit abdominal panniculus, and the lowest pHt values observed (approximately pH 6.5; Fig. 4, group IIIG) were close to those observed with tissue hypoxia in the rabbit abdominal panniculus (18).

It is not known whether the decreases in pHt observed in this study occur when similar solutions of equivalent volume are injected in humans. Although the pH of most clinically used local anesthetic solutions is higher than 5.0, it is lower than that in some (19). The volume of solution used (0.4 ml in a 500-g rat) is equivalent to a 28-ml injection in a 70-kg human, well within the range of clinically used volumes for some peripheral nerve blocks. It may be argued that when such solutions are used in humans they are injected into areas whose vascularity would minimize decreases in pHt. When epinephrine-containing solutions at both pH 5.0 and 7.4 were injected into the infraorbital region, a relatively vascular area, pHt decreased with both solutions (Fig. 2, group IIB; group IID) and was significantly different from that seen with epinephrine-free solutions (Fig. 2, group IIA vs group IIB; group IIC vs group IID). If comparable changes in pHt occur in clinical practice it might caution against the use of acidic epinephrine-containing solutions, because such decreases in pHt have been noted to be associated with tissue hypoxia (18), which could possibly contribute to the rare occurrence of localized tissue toxicity of local anesthetics.

In summary, in a standardized comparison of local anesthetic solutions at pH 5.0 and 7.4 with and without epinephrine, alkaline solutions did not produce a significant prolongation of local anesthetic action. Acidic solutions decreased pHt at the site of injection, the greatest and most prolonged decreases were produced when epinephrine was present in the injectate.

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## Pulmonary and Systemic Hemodynamic Responses to Fentanyl in Infants

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HICKEY PR, HANSEN DD, WESSEL DL, LANG P, JONAS RA. Pulmonary and systemic hemodynamic responses to fentanyl in infants. *Anesth Analg* 1985;64:483-6.

*Pulmonary and systemic hemodynamic responses to fentanyl were studied in 12 infants after repair of congenital heart defects. During controlled ventilation, hemodynamic responses to 25  $\mu$ g/kg of fentanyl were measured. No significant changes were found in heart rate, cardiac index,*

*mean pulmonary artery pressure, or pulmonary vascular resistance index 5 min after the fentanyl had been given. There were small but statistically significant decreases in mean arterial pressure and systemic vascular resistance index after fentanyl. We conclude that under the conditions of this study, pulmonary and systemic hemodynamics in infants are minimally altered by 25  $\mu$ g/kg of fentanyl.*

**Key Words:** ANALGESICS—fentanyl. ANESTHESIA—pediatric cardiovascular.

Fentanyl use in large doses for the anesthetic management of small children is becoming widespread. Safe induction of anesthesia with fentanyl in sick infants with decreased myocardial reserve has been documented in several studies where only minimal changes occurred in heart rate and systemic arterial pressure (1,2). However, the hemodynamic responses of the infant to fentanyl have not been studied. The more traditional anesthetic agent for small children, halothane, has been shown to cause bradycardia, hypotension, and myocardial depression even in infants with normal cardiovascular systems (3,4). These circulatory effects appear to be due to halothane's rapid uptake and distribution in infants (5) and to the recently documented sensitivity of the neonatal and infant myocardium to the myocardial depressant effects of halothane (6-8). Because fentanyl in large doses, on the contrary, appears to cause minimal disturbance of blood pressure and heart rate even in infants with severe cardiac disease, more detailed information on the hemodynamic effects of fentanyl

in this age group is needed to confirm and extend the previous limited studies of fentanyl's cardiovascular effects in children.

Previous studies raised the question of possible beneficial effects of fentanyl on the pulmonary circulation in infants but provided no data to answer this question (2,9). Although changes in the pulmonary circulation are especially important in sick neonates and in all children with congenital heart disease, no data about the effects of fentanyl on the pulmonary circulation in the infant are available. Numerous studies in adults have shown minimal effects of large doses of fentanyl on systemic hemodynamics, but the effects of fentanyl on the pulmonary circulation have not specifically been studied, even in adults (10-16). In the few studies where pulmonary vascular resistance has been measured incidentally during administration of fentanyl in adults, the results were variable (12,17,18). Therefore, the purpose of our study was to measure the pulmonary and systemic circulatory responses of infants to a moderately large dose of fentanyl.

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### Methods

The study protocol was approved by the institutional Committee on Clinical Investigation, and informed consent was obtained from the parents of the infants included in the study. We studied 12 infants when they had become responsive in the intensive care unit after operative repair of congenital heart disease. Age,

Table 1. Age, Weight, and Diagnosis of Study Infants

Age (months)	Weight (kg)	Diagnosis
10	6.8	VSD
4	5.8	VSD
4½	6.6	TOF
4	5.4	TGA
5½	4.6	CAVC
8	5.2	VSD
5	4.3	VSD
10	6.2	CAVC
10	7.7	TOF
6	5.6	CAVC
12	7.7	CAVC
7	5.5	CAVC
7 (±3.5)	6.0 (±1)	Mean (±SD)

Abbreviations: VSD, ventricular septal defect; CAVC, complete atrio-ventricular canal; TOF, tetralogy of Fallot; TGA, transposition of the great arteries.

weight, and diagnosis for these patients are shown in Table 1. Only hemodynamically stable infants not requiring inotropic support were studied. Indwelling right and left atrial, pulmonary artery, and radial artery catheters were inserted during the operation, along with a separate pulmonary artery thermistor. Post-operative chest x-rays and pressure tracings confirmed the position of the intrathoracic catheters. Pulmonary arterial saturations of less than 80% or normal indocyanine green dye studies confirmed the absence of residual intracardiac shunts.

All infants received approximately 50 µg/kg of fentanyl for anesthesia prior to cardiopulmonary bypass and subsequent deep hypothermic circulatory arrest; no further fentanyl was given until the time of the study. They were being mechanically ventilated with an  $FI_{O_2}$  of at least 0.5 at the time of this study, which was generally 5–7 hr after the operation. Arterial blood gas tensions were obtained during the study in each infant. The mean arterial blood pH for the group was  $7.47 \pm 0.05$  (SD), the mean  $PaCO_2$  was  $37 \pm 5$ , and the mean  $PaO_2$  was  $154 \pm 53$ .

Baseline measurements of left and right atrial, mean pulmonary and systemic arterial pressures were obtained, and a thermodilution cardiac output was determined by injecting either 1 or 3 ml of 5% dextrose solution ( $0^\circ C$ ) through the right atrial catheter. The volume of injectate depended upon the infant's weight. Thermodilution curves were examined, and three determinations of cardiac output were obtained for each measurement period. Successive cardiac output determinations were generally within 5% of each other and always within 10%.

Fentanyl, 25 µg/kg, was given over 1–2 min intravenously along with a small dose of pancuronium to prevent rigidity (0.015 mg/kg). Repeat measurements

of the above variables were obtained 3–5 min after fentanyl. Cardiac index (CI) was calculated in each infant using body surface areas derived from a computer program based upon height and weight. Pulmonary vascular resistance index (PVRI) and systemic vascular resistance index (SVRI) in Wood units ( $mm\ Hg \cdot L^{-1} \cdot min \cdot m^2$ ) were calculated from the CI and pressure data for each infant. Mean values and standard deviation of each variable were calculated, and the paired *t*-test was used to compare changes after administration of fentanyl. A *P* value of  $< 0.05$  was considered statistically significant.

## Results

The results are shown in Table 2. No significant changes were found in heart rate, left atrial pressure (LAP), mean pulmonary arterial pressure (MPAP), pulmonary vascular resistance index (PVRI), or CI after administration of fentanyl. Small decreases occurred in the mean systemic arterial pressure (MAP) and the systemic vascular resistance index (SVRI), along with a small increase in the right atrial pressure (RAP). These changes were statistically significant at the 0.05 level, but too small to be important clinically.

No one infant had any unusual hemodynamic response to the fentanyl. In Table 2 there is little difference in each variable between the standard deviation of the control measurement and the standard deviation after fentanyl was given. Thus there was minimal variability in the response of the study population to fentanyl; individual responses to fentanyl varied little from the mean in this small group of infants.

## Discussion

The hemodynamic responses of our infants to a large dose of fentanyl are within the range of those reported in adult patients at this and higher dose levels of fentanyl (10–18). The present findings confirm the relative stability of heart rate and systemic blood pressure after large doses of fentanyl reported in the study of Robinson and Gregory in premature neonates (1), and in our previous study of infants with congenital heart disease (2). Our present data document the lack of any appreciable depression of cardiac performance in infants given fentanyl, because cardiac index was well maintained without any change in preload (LAP) and with only a minimal decrease in afterload (MAP). Additionally these data document the stability of SVRI and PVRI after fentanyl in infants.

The small decrease in MAP found in this study was also found in infants given larger doses of fen-



Table 2. Hemodynamic Responses to  $\mu\text{g/kg}$  of Fentanyl (mean  $\pm$  SD)

Variable	Before fentanyl	After fentanyl
Heart rate (beats/min)	116 $\pm$ 17	116 $\pm$ 21
MAP (mm Hg)	74 $\pm$ 14	70 $\pm$ 17 <sup>a</sup>
RAP (mm Hg)	8 $\pm$ 3	9 $\pm$ 3 <sup>a</sup>
MPAP (mm Hg)	20 $\pm$ 7	20 $\pm$ 7
LAP (mm Hg)	10 $\pm$ 3	11 $\pm$ 4
CI ( $\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ )	2.8 $\pm$ 0.7	2.9 $\pm$ 0.7
PVRI (Wood units)	3.4 $\pm$ 2	3.3 $\pm$ 2
SVRI (Wood units)	24 $\pm$ 7	22 $\pm$ 7 <sup>a</sup>

<sup>a</sup> $P < 0.05$ .

tanyl (50 and 75  $\mu\text{g/kg}$ ) in our previous study (2), and was also found in adults given similar doses of fentanyl (20–30  $\mu\text{g/kg}$ ) (10). Because CI was unchanged in the present study, the small decrease in SVRI after fentanyl in our infants accounts for the slight decrease seen in the MAP. Although SVRI data have not been previously reported in infants given fentanyl, similar small decreases in SVRI with unchanged CI have been reported in adults with compromised ventricular function who were given a similar dose of fentanyl (30  $\mu\text{g/kg}$ ) (12).

Previous studies of adults have not focused on the changes in the pulmonary circulation with fentanyl; both increases and decreases in PVR have been found incidentally in adults given fentanyl (12,17,18). Our previous study of fentanyl in infants undergoing surgery for congenital heart disease provided indirect evidence that there might be a decrease in PVRI with fentanyl, but pulmonary hemodynamics could not be measured in that study (2). In the present study there was no change in the resting PVRI of our infants after fentanyl was given. The infants were being ventilated at an  $\text{FI}_{\text{O}_2}$  of greater than 0.5 and had high  $\text{PaO}_2$  levels at the time of the study, so that perhaps the pulmonary vascular bed was near maximally dilated by hyperoxia and little further decrease in PVRI was possible. Although the mean value of PVRI in our infants (three Wood units) is at the upper limits of the normal range in adults, this PVRI is well within the normal range for a group of infants most of whom previously had increased pulmonary blood flow resulting from left-to-right intracardiac shunting. The relatively large variability in the PVRI data results from the inclusion of both patients with left-to-right shunting and patients with right-to-left shunting in the study. This was done to make the results more relevant to the general population of infants who have no history of increased pulmonary blood flow.

The extent to which our findings apply to the larger doses of fentanyl used clinically in children, such as

50 or 75  $\mu\text{g/kg}$ , might be questioned. However, several lines of evidence suggest that our findings may be extrapolated to these higher doses. First, the magnitude and direction of changes in blood pressure and heart rate reported in the previous study of infants given 50 and 75  $\mu\text{g/kg}$  of fentanyl (2) were very similar to those found in the present study. In addition, the hemodynamic effects of fentanyl in adults at doses ranging from 20 or 30  $\mu\text{g/kg}$  to 150  $\mu\text{g/kg}$  differ little from each other and are similar to our present findings in infants given 25  $\mu\text{g/kg}$  (10–12,14,17). Lunn et al. reported no further hemodynamic changes in adults when fentanyl doses were increased beyond 25  $\mu\text{g/kg}$  (18). Furthermore, recent data on the pharmacokinetics of fentanyl in children indicate that plasma fentanyl concentrations are up to 300% greater than those found in adults given a similar dosage and that a bolus dose in the range of 30  $\mu\text{g/kg}$  gives effective plasma levels of fentanyl in small children (19). Thus the doses of fentanyl we used for this study in infants might well have produced plasma levels similar to those observed in adults given 50 or 75  $\mu\text{g/kg}$  doses of fentanyl.

Although we did not measure fentanyl levels prior to the study, the study of Koren et al. (19) shows that fentanyl plasma levels were approximately 5 mg/ml at the end of cardiopulmonary bypass in young children previously given 50  $\mu\text{g/kg}$ . Thus at the time of our study, 6–8 hr after the end of bypass, it is very unlikely that clinically significant plasma levels of fentanyl were present in our infants.

Salmenpera et al. (20) recently demonstrated that pancuronium (0.1 mg/kg), in contrast to vecuronium, reverses decreases in heart rate and CI caused by fentanyl in adults. Their study raises the question of how much the effects of fentanyl in the present study are modified by the concomitant use of pancuronium. In an effort to avoid this issue, we used only a small dose of pancuronium to prevent the risk of chest wall rigidity with fentanyl, a problem that we have seen in infants in the operating room. This dose of pancuronium, 0.015 mg/kg, is generally not associated with increases in heart rate when given alone (21). Furthermore, in children with congenital heart disease, a much larger dose of pancuronium (0.100 mg/kg) given during anesthesia did not result in a significant increase in heart rate at 3–5 min after administration (22), making it unlikely that the small dose of pancuronium we used could by itself explain the lack of decrease in heart rate and CI with fentanyl in our study. In contrast however, Bovill et al. (23) state that small doses of pancuronium attenuate the bradycardia induced by fentanyl. All these considerations aside, we do not advocate use of these doses of fentanyl in

infants or children without concomitant use of pancuronium because of the clear danger of chest wall rigidity and the possible danger of bradycardia.

If the small dose of pancuronium used does not explain the absence of decreases in heart rate in our infants given fentanyl, this finding might be explained by poor development of cardiac sympathetic nerves in young infants (24,25). In young infants with immature development of cardiac sympathetic innervation, fentanyl-induced suppression of the sympathetic nervous system might be less effective in producing bradycardia.

Although this study was carried out relatively early in the postoperative period when the myocardium might still have been depressed, this would be expected to exaggerate any deleterious changes in hemodynamics with fentanyl. Thus although we did not study infants with severe postoperative myocardial depression who required inotropic support, we expect that our study would tend to overestimate the detrimental hemodynamic effects of fentanyl in infants.

We conclude from our present study that baseline hemodynamics in both the pulmonary and systemic circulations of infants are only minimally altered by fentanyl given with a small dose of pancuronium. However, the hemodynamic responses after fentanyl to surgical stimulation and other forms of stress were not studied. Although our initial study of fentanyl in infants (2) and studies in adults (10-18) all show that hemodynamic responses to stress are attenuated by fentanyl, the effect of fentanyl on the response of the pulmonary circulation to stress in the infant remains to be specifically studied. Given the critical role of the pulmonary circulation in children with congenital heart disease and in all neonates undergoing surgery, studies of the effects of anesthetic agents on stress responses in the pulmonary circulation may yield much useful information.

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## Liver Function in Patients with Mild Alcoholic Hepatitis, after Enflurane, Nitrous Oxide–Narcotic, and Spinal Anesthesia

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*The effects of three anesthetic techniques on liver function were compared in patients with mild alcoholic hepatitis who required surgery, both peripheral and superficial. Thirty patients were randomly assigned to receive one of three anesthetics: 1) thiopental, nitrous oxide and oxygen, enflurane, plus muscle relaxant; 2) thiopental, nitrous oxide and oxygen, narcotic, plus muscle relaxant; or 3) spinal anesthesia with tetracaine. Measurements of hepatic function were made preoperatively (on the day of operation) and on the first and third postoperative days. Levels of serum*

*bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and lactate dehydrogenase liver isoenzyme were similar in the three groups on both postoperative days. They were not significantly different from those obtained preoperatively, although mean values decreased by the first postoperative day and again on the third. The data suggest that the choice among the three anesthetic methods studied could be based on factors other than the presence of mild alcoholic hepatitis and that, when peripheral surgery is required, one may not anticipate a worsening of any biochemical disorder in the first three postoperative days.*

**Key Words:** ALCOHOL. LIVER—disease, function.

Heavy ingestion of alcohol is relatively common in patients requiring surgery and is a factor in many types of trauma. Frequently the liver is enlarged and serum levels of bilirubin and liver enzymes may be higher than normal. These patients may be at risk of significant morbidity and mortality (1–4), and there is concern that at least some anesthetics may aggravate preexisting liver disease. Mikkelsen et al. (5) reported four postoperative deaths from hepatic failure among ten patients with severe alcoholic hepatitis. In patients with a different type of acute liver disease, Harville and Summerskill (6) reported a 9.5% mortality in patients with viral hepatitis who had exploratory laparotomy. However, there is little information concerning the risk of surgery and anesthesia for patients having milder cases of acute alcoholic liver disease, or for this type of patient undergoing surgery not involving abdominal exploration (7).

Patients with mild alcoholic hepatitis may have minimal clinical evidence of hepatic disease, but he-

patic biopsies show steatosis, fibrosis, and necrosis of the liver (2,8–10). Such patients seem to have a relatively good postoperative prognosis (2,8,9). Several investigators (11–13) have described the reversible nature of most cases of alcoholic liver disease when abstinence is practiced and diet controlled. Thus because there is potential for improvement in this disorder, a further hepatic insult should be avoided during the reparative process. Frequently, surgery is delayed until biochemical values are normal or stable. We examined changes in hepatic function tests in patients with mild alcoholic hepatitis when there was no such delay before elective or semielective surgery.

### Methods

Patients selected for study required surgery that was both peripheral and superficial and had a history of heavy alcohol ingestion. In addition, two or more of the following conditions were present: hepatomegaly greater than 10 cm below the costal margin; or increased serum levels of bilirubin, glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), or lactate dehydrogenase (LDH) liver isoenzyme. Patients were excluded if any of the following conditions were present: evidence of alternate causes of liver abnormality, such as a history of biliary tract disease, sepsis, gastrointestinal bleeding, congestive

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heart failure; a prothrombin time that represented less than 50% of the normal activity; a serum bilirubin level greater than 5 mg/dl for six consecutive days; an abnormal value for blood urea nitrogen (BUN); or current evidence of encephalopathy. This study was approved by our institutional committee on human research, and informed consent was obtained from all patients.

Thirty patients were assigned randomly to receive one of three types of anesthesia: thiopental, 60% nitrous oxide in oxygen, enflurane, muscle relaxant, and controlled ventilation; thiopental, 60% nitrous oxide in oxygen, narcotic, muscle relaxant, and controlled ventilation; or spinal anesthesia with tetracaine (for lower-extremity surgery). Blood was obtained preoperatively (on the day of operation) and on the first and third postoperative days for laboratory measurements of serum levels of bilirubin, SGOT, SGPT, and LDH liver isoenzyme (14). In addition, values for hemoglobin, white blood cell count, BUN, prothrombin time, and serum albumin were determined preoperatively (Table 1). Dilutions of commercial standards were used to determine prothrombin time-activity curves, to detect those patients whose prothrombin activity was less than 50% of normal (15).

The surgery performed included eleven open leg or arm orthopedic procedures, five facial fracture reductions, three minor ENT procedures, four perineal operations, five minor plastic excisions or grafts and one each, mastectomy and incision and drainage of hand abscess. The duration of anesthesia ranged from 30 min to 5 hr.

Data were compared using one-way analysis of variance and Newman-Keuls multiple range tests. Absolute values for each day and each agent were compared, as were changes by day and by type of anesthesia. Statistical significance was assumed for probability levels less than 5%.

## Results

Mean biochemical values for the three groups of patients are shown in Table 2. Although the mean serum bilirubin level in patients given narcotics was normal, all other mean values were abnormal preoperatively and there was no statistical difference between any of these means. Of 30 patients studied, 26 had preoperative abnormalities in three of the following variables: liver size, bilirubin, SGOT, SGPT, and LDH isoenzyme. Fourteen patients had four abnormalities, and two had five. In 21 patients, the ratio of SGOT to SGPT was greater than 2:1. The overall clinical evaluation of the group was that they had mild al-

Table 1. Preoperative Values in 30 Patients with Mild Alcoholic Hepatitis

Variable	Mean $\pm$ SD
Age (yr)	43 $\pm$ 11
Hemoglobin (g/dl)	12.4 $\pm$ 2.1
White blood cells (1000/mm <sup>3</sup> )	8.2 $\pm$ 2.2
Blood urea nitrogen (mg/dl)	10 $\pm$ 5
Prothrombin time (sec)	10.9 $\pm$ 1.1
Serum albumin (g/dl)	3 $\pm$ 0.7

coholic hepatitis at the time of surgery (the single exception, with enflurane, is described below).

The mean values for serum bilirubin, SGOT, SGPT, and LDH were less than those obtained before the operation, on the first postoperative day, and again on the third. However, there was no statistically significant difference between any of the values, or the magnitudes of change.

One patient given enflurane died on the ninth postoperative day. He was admitted with hepatic encephalopathy and underlying hepatic cirrhosis 24 days before the operation. Encephalopathy was corrected with therapy but ascites occurred. The surgical procedure, which consisted of direct laryngoscopy (to investigate hoarseness) with controlled ventilation through an endotracheal tube, was uneventful. Five days after the operation, encephalopathy recurred with seizures. At this time, serum electrolytes, arterial blood gas values, and cerebrospinal fluid pressure were within normal limits. Since the laryngoscopy, liver function tests had improved or remained unchanged. On the third postoperative day, these values were as follows: SGOT, 79 IU/L; SGPT, 59 IU/L; serum bilirubin, 1.8 mg/dl; LDH, 230 IU/L with liver isoenzyme 15%. On the seventh postoperative day, fecal soiling of the ascitic fluid was noted but operative intervention was not attempted, and death from hepatorenal failure associated with sepsis occurred two days later. Although this patient met the criteria for admission to the study at the time of surgery, the degree of liver disease was clearly greater than that in the other patients. The cause of death was believed to be unrelated to anesthesia, as all his laboratory values had improved by the third postoperative day and had not worsened at the time of his clinical deterioration.

## Discussion

The clinical syndrome of acute alcoholic liver disease, characterized by hepatomegaly, jaundice, abnormal liver function tests, and a history of acute alcoholism, is associated with high morbidity and mortality (1,3). When correlated with pathologic findings, this syn-

Table 2. Liver Function Tests and Type of Anesthesia<sup>a</sup>

Sequence <i>n</i>	Day of operation (before the operation)			Postoperative Day 1			Postoperative Day 3		
	S	N	E	S	N	E	S	N	E
	5	12	13	5	12	13	5	12	13
Serum bilirubin (mg/dl) (normal, < 1.3 mg/dl)									
Mean	1.7	1.1	1.8	1.6	1.1	1.7	1.5	0.8	1.5
SD	1.9	1.2	2.4	2.0	0.8	2.0	1.8	0.7	1.7
Serum glutamic oxaloacetic transaminase (IU/L) (normal, < 50 IU/L)									
Mean	97	150	114	94	104	103	105	68	82
SD	49	119	67	51	71	69	67	38	42
Serum glutamic pyruvic transaminase (IU/L) (normal, < 23 IU/L)									
Mean	27	64	48	28	52	39	27	38	31
SD	16	61	41	16	47	31	11	40	25
Total lactate dehydrogenase (IU/L)/isoenzyme (%) (normal, < 180 IU/L and < 16%)									
Mean	181/17	219/26	254/21	167/16	186/20	227/16	174/16	182/18	203/17
SD	74/7	50/8	165/9	60/7	46/7	115/8	60/9	55/6	88/5

<sup>a</sup>Abbreviations: S, spinal anesthesia with tetracaine; N, nitrous oxide, narcotic, oxygen, relaxant; E, enflurane, nitrous oxide, oxygen.

drome has been called alcoholic hepatitis (2), steato-necrosis (16), and hyaline necrosis (4). Clinical signs indicating a poor prognosis include marked hyper-bilirubinemia (1), increased blood urea nitrogen (1,16), marked leukocytosis (1), and marked increase in prothrombin time (1,2,16). Such patients were excluded from this study, which was intended to examine the effects of anesthesia on a less advanced stage of alcoholic hepatitis. The consumption of alcohol in our study group varied from a pint of liquor to a case of beer a day, in some instances for many years.

Any concern that mild alcoholic hepatitis might be exaggerated by anesthesia and peripheral surgery stems not only from changes seen in patients with severe hepatic injury but also from other less specific data. The mechanism for any hepatic damage produced by anesthetics remains unknown, although the subject has been studied extensively (17,18). In most cases of postoperative hepatic necrosis, however, complicating clinical conditions are noted, such as sepsis, shock, or preexisting liver disease (19,20). Under experimental conditions using laboratory animals, hypoxemia may be an important factor (21).

Numerous investigators have examined the effects of anesthesia on liver function in patients without liver disease. After general anesthesia (22-26) and even spinal anesthesia (22,23), frequent small and transient increases have occurred in serum enzyme levels. General anesthesia without surgery is associated with minimal or no increases in SGOT, serum ornithine carbamoyl transferase (SOCT), or SGPT in normal man (22,27,28). Brohult and Gillquist (22) found, however, increased levels of SOCT after hypotension occurring during spinal anesthesia.

Hepatic blood flow may be altered in different ways

by different anesthetics. Decreases in hepatic blood flow due to halothane (29) and cyclopropane (30) are well known. Similar decreases are caused by spinal anesthesia (31). During normocarbica, nitrous oxide and muscle relaxants have little effect on hepatic blood flow (32). Decreases are more likely during surgery of the upper abdomen (33).

Thus, in any patient, multiple factors may affect both hepatic blood flow and function during and after anesthesia. Most postoperative changes in hepatic function are not specific to any one anesthetic but rather to factors such as abnormal blood-gas tensions, decreases in hepatic blood flow, differences in operative site, and significant systemic disease. Overall, in normal patients, the incidence of serious hepatic damage from anesthetics is extremely low (19).

The apparent lack of harmful effect from the anesthetics used in this study must be interpreted with caution. The number of patients studied was small, as was the magnitude of the preoperative liver disease, at least as reflected by the tests of hepatic function we used. The one death from late sepsis and liver failure was in a patient with a major degree of preoperative liver disease characterized by encephalopathy despite relatively small abnormalities in standard laboratory tests. This highlights the importance of not using laboratory data as the sole basis for characterizing "mild alcoholic hepatitis." Certainly, such data cannot be used as the sole basis for decisions relating to patients requiring thoracic or abdominal surgery. Indeed, anesthetics that are not harmful when used for peripheral, superficial operations may have different effects on postoperative hepatic function after upper-abdominal surgery, a type of surgery in which hepatic blood flow is decreased. However, our data

do suggest that the practice of delaying peripheral, superficial surgery in patients with liver function abnormalities within the range studied should be reconsidered. In choosing an anesthetic for such patients, no apparent deleterious effect on these abnormalities is produced by spinal anesthesia or by the general anesthetic techniques we studied. Anesthetic technique for patients such as those we studied should probably be selected on the basis of factors other than the presence of biochemical criteria of acute alcoholic hepatitis.

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# Successful Cardiovascular Resuscitation after Massive Intravenous Bupivacaine Overdosage in Anesthetized Dogs

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KASTEN GW, MARTIN ST. Successful cardiovascular resuscitation after massive intravenous bupivacaine overdosage in anesthetized dogs. *Anesth Analg* 1985;64:491-7.

*We investigated whether anesthetized dogs (n = 6) could be resuscitated from massive cardiovascular toxic intravenous bupivacaine overdoses. Five mg/kg of bupivacaine was given into the right atrium over 10 sec every minute until cardiac collapse occurred. At the same time the bupivacaine was given, the animals were made apneic for 90 sec (to mimic the clinical situation in which seizures often render patients apneic) and then ventilated with 100% oxygen. After bupivacaine administration, cardiovascular collapse occurred in the form of ventricular tachycardia, or more*

*commonly, electromechanical dissociation. Resuscitation was performed using open-chest heart massage, bretylium for ventricular tachycardia, and epinephrine with atropine for electromechanical dissociation and bradycardia. After successful resuscitation, each animal was again given bupivacaine as above until cardiovascular collapse occurred and resuscitation was performed again. Each dog underwent three arrests and resuscitations. The total cumulative bupivacaine dose was  $64.1 \pm 26.8$  mg/kg. We conclude that anesthetized dogs receiving massive cardiovascular toxic doses of bupivacaine can be resuscitated easily and consistently with appropriate therapy.*

Key Words: ANESTHETICS, LOCAL—bupivacaine.

There has been much interest recently in the untoward cardiovascular (CV) effects of potent long-acting local anesthetics such as bupivacaine (BUP) and etidocaine (1,2). Liu et al. examined the CV toxicity of intravenous local anesthetics in ventilated dogs anesthetized with pentobarbital, but they did not attempt to resuscitate the animals after CV collapse occurred following a cumulative dose of  $20.4 \pm 2.4$  mg/kg of BUP (3). Thigpen et al. (4) reported that 4.2 mg/kg of intravenous BUP resulted in CV collapse in hypoxic and acidotic sheep, none of which could be resuscitated by pharmacologic therapy and chest massage. Case reports that describe sudden CV collapse without apparent prior hypoxia (5,6), led several investigators to study the CV changes associated with toxic doses of these local anesthetics (7,8). However, few detailed studies have determined whether animals can be resuscitated from the CV toxicity. Because it has been claimed that CV toxicity of these local anesthetics is difficult to treat (1,2,6), this investigation was undertaken to examine whether or not dogs can

be resuscitated after massive BUP overdosage resulting in CV collapse.

## Methods

The study received approval from the animal experimentation committee. Six adult mongrel dogs of either sex, weighing  $20.9 \pm 1.7$  kg each, were anesthetized with 2 mg/kg intravenous ketamine and paralyzed with 0.15 mg/kg pancuronium bromide. The animals were placed in the supine position on the laboratory table. They were intubated with an 8-mm inside diameter cuffed endotracheal tube. Ventilation was provided with a Harvard animal respirator using room air. A percutaneous 16-gauge arterial catheter in the femoral artery provided blood samples to measure gas tensions and record arterial blood pressure. A 14-gauge right atrial catheter was placed via the right external jugular vein after the vein was exposed by a surgical incision. Using pressure wave monitoring, the catheter was advanced into the right atrium and not beyond into the right ventricle. Cardiac rate and rhythm using lead II electrocardiograms (ECG) were recorded. A median sternotomy and pericardotomy were performed to allow open-chest heart massage. Beginning and ending hematocrits were measured.

The ECG, cardiac rhythm, heart rate, right atrial pressure, systolic blood pressure, diastolic blood

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pressure, and mean arterial pressure were measured and recorded throughout the experiment (Grass model 7 polygraph). While the animals were being ventilated with an  $\text{FI}_{\text{O}_2}$  of 0.21, arterial blood gas tensions were maintained within the physiologic range (pHa 7.35–7.45,  $\text{PaCO}_2$  35–45 mm Hg, and  $\text{PaO}_2$  50–90 mm Hg) as nearly as possible by adjusting the respiratory rate and tidal volume. Fluid administration and urine output were measured and recorded. The times of administration and dosage of all drugs given were recorded directly on the polygraph record. The time intervals from the beginning of resuscitation during the CV collapse to the restoration of baseline blood pressure were recorded.

To determine the CV effects of the hypoxia due to apnea alone, four of the six animals were made apneic for 90 sec by disconnecting the ventilator from the endotracheal tube prior to administering bupivacaine. At the end of 90 sec, arterial blood gas tensions were measured and the animal was ventilated again with an  $\text{FI}_{\text{O}_2}$  of 0.21 at the same rate and tidal volume. The ECG, arterial pressure, right atrial pressure, and arterial blood gases were monitored until they returned to baseline levels.

The infusion of lactated Ringer's solution was adjusted frequently to maintain right atrial pressure in the range of 4–10 mm Hg. Bupivacaine was administered via the central venous catheter into the right atrium at a dose of 5 mg/kg over 10 sec every minute until ventricular tachycardia or severe bradycardia with electromechanical dissociation and blood pressure became zero. Severe bradycardia was defined as at least a 60% decrease from baseline heart rate. To mimic the respiratory conditions after clinical seizures that often render patients apneic, the animals were made apneic for 90 sec after the first dose of BUP by disconnecting the ventilator from the endotracheal tube to make the animals hypoxic. After the 90-sec period of apnea had elapsed, arterial blood gas tensions were measured and the animals then were ventilated with 100% oxygen. If CV collapse had not occurred at this point, BUP was continued at 5 mg/kg over 10 sec every minute until collapse occurred.

Treatment of cardiac collapse was as follows. Ventricular tachycardia: bretylium, 30 mg/kg, was given as 5 mg/kg every 30 sec intravenously through the central venous catheter.

Severe bradycardia with electromechanical dissociation: epinephrine, 0.75 mg, and atropine, 0.8 mg, was given intravenously through the central venous catheter initially followed by 0.5 mg epinephrine and 0.4 mg atropine every 45 sec until return of stable rhythm and blood pressure. Additional atropine, 0.5 mg, was given at the end of the resuscitation if the heart rate was not at baseline.

Intravenous sodium bicarbonate was given after resuscitation if arterial blood samples showed evidence of metabolic acidosis; the dose was calculated based on the base deficit using standard formulas. All animals received open-chest heart massage after the blood pressure decreased to zero. Fluid administration after the resuscitation was continued with lactated Ringer's solution to maintain right atrial pressure between 4–10 mm Hg.

To challenge the ability to resuscitate animals given CV toxic doses of BUP, the BUP dosing regimen was resumed after blood pressure returned to baseline levels for at least 5 min without the need for additional pharmacologic support. The experimental cycle of BUP-induced CV collapse, followed by resuscitation, was repeated until three resuscitations had been achieved. The animals were sacrificed with KCl, 100 mEq, intravenously after the final resuscitation when at least 15 min had elapsed without the need for pharmacologic support.

The BUP used was commercially available 0.75% preservative-free solution. Epinephrine and atropine solutions were from commercially available multiple-dose vials. Sodium bicarbonate and bretylium were from single-dose commercially available ampules.

Data were compared using analysis of variance and Student's *t*-test. A probability level of less than 0.05 ( $P < 0.05$ ) was considered statistically significant.

## Results

In the control period, the animals developed sinus bradycardia and arterial hypertension after the 90-sec period of apnea. The mean decrease in heart rate was  $52 \pm 15\%$  from baseline and the increase in mean arterial pressure was  $30 \pm 12\%$ . These changes were statistically significant. In contrast, when the apneic animals were given BUP, they developed either ventricular tachycardia with greatly diminished blood pressure or a slow idioventricular rhythm with broad QRS complexes and hypotension consistent with electromechanical dissociation. None of the animals developed ventricular fibrillation. The differences in blood pressure and heart rate between the apnea plus BUP and apnea-only exposures were statistically significant. The pHa,  $\text{PaCO}_2$ , and  $\text{PaO}_2$  changes induced by apnea were not significantly different between the two exposures (Table 1). Ventricular tachycardia of greater than 30-sec duration occurred in two of the six animals immediately after the first dose of 5 mg/kg of BUP. The remaining sixteen BUP administrations resulted in electromechanical dissociation. Thus in four of the animals, all three administrations resulted in electromechanical dissociation; in the other two this occurred on the second and third administrations of

Table 1. Arterial Blood Gas Tensions, pH, and Base Excess

Group	FiO <sub>2</sub>	PaO <sub>2</sub> (mm Hg)	PaCO <sub>2</sub> (mm Hg)	pH	Base excess (mEq/L)
Control prior to apnea	0.21	70.7 (54.5-94.5)	32.5 (26.4-38.6)	7.41 (7.36-7.45)	-3.0 (-7.0-+1.3)
Control after apnea	0.21	29.1 (28.2-32.2)	38.5 (33.2-43.2)	7.36 (7.31-7.40)	-5.0 (-2.0--9.0)
Bupivacaine prior to apnea	0.21	52.6 (40.9-64.9)	35.0 (26.1-42.3)	7.40 (7.31-7.51)	-2.3 (-1.1--4.2)
Bupivacaine after apnea	0.2	22.8 (14.5-28.1)	39.4 (33.1-49.5)	7.35 (7.30-7.45)	-4.0 (-1.0--5.3)
Bupivacaine after resuscitation	1.0	221.7 (83.7-425.1)	36.1 (30.1-48.7)	7.42 (7.27-7.53)	-1.8 (-1.0--4.6)

Values given as means (ranges).

BUP. Mean arterial pressure was unobtainable after administration of BUP, and all of the animals required brief (1-2 min) open-chest heart massage during each resuscitation attempt.

Each of the six animals received three doses of BUP for a total of eighteen episodes of CV collapse. The doses given for the first, second, and third episodes were  $23.3 \pm 16.0$ ,  $25.8 \pm 17.4$  and  $15.0 \pm 5.5$  mg/kg, respectively (Table 3). There is no significant difference between the three doses. The cumulative dose was  $64.1 \pm 26.8$  mg/kg over a period of  $41.4 \pm 10.2$  min after three episodes of CV collapse and resuscitation. There are no significant differences in blood pressure and heart rate that resulted from BUP administration in the three doses given (Table 2). The differences in post-resuscitation blood pressure and baseline are not significant among the three resuscitations; however, the differences between post-resuscitation and baseline heart rate are significant (Table 2). The heart rate tended to be slower after each resuscitation despite return to baseline blood pressure. All animals survived three successive episodes of CV collapse from BUP.

Two animals went into sustained ventricular tachycardia after the initial dose of BUP, but a dose of 30 mg/kg of bretylium restored sinus rhythm. Neither these nor the other animals developed ventricular tachycardia after subsequent administration of BUP. Direct counter-shock was not required. Slow idioventricular rhythm with electromechanical dissociation was the most common arrhythmia, occurring in sixteen of eighteen drug administrations; this responded promptly to epinephrine and atropine. There is no significant difference between the doses used in the first, second, and third resuscitations (Table 4). The time intervals from beginning of resuscitation until restoration of baseline blood pressure were  $1.4 \pm 0.5$ ,  $2.2 \pm 1.3$ , and  $3.8 \pm 3.3$  min for the three attempts at resuscitation (Table 3). There is no significant difference among the three time intervals, al-

though the trend was for slightly longer intervals in the second and third attempts. The volume of crystalloid given was  $104 \pm 42$  ml·kg<sup>-1</sup>·hr<sup>-1</sup> during the experiment. This amount was necessary to maintain right atrial pressure in the 4-10 mm Hg range. Urine output was  $7.7 \pm 2.9$  ml·kg<sup>-1</sup>·hr<sup>-1</sup>. The starting hematocrit was  $44.2 \pm 8.0\%$  and ending was  $36.0 \pm 8.3\%$ .

All animals survived a total of eighteen episodes of profound CV collapse after intravenous administration of BUP. Each resuscitation resulted in a stable blood pressure without need for additional pharmacologic intervention. The post-resuscitation electrocardiogram showed a sinus rhythm with a broadened QRS complex, indicating that a conduction disturbance was still present. This was a stable rhythm that allowed for return of blood pressure and arterial waveform configurations to baseline.

## Discussion

The purpose of this investigation was to determine whether dogs receiving CV toxic doses of BUP could be resuscitated. Our results show that anesthetized apneic dogs experienced profound CV depression after massive intravenous doses of BUP. The CV collapse can be easily and rapidly corrected with appropriate pharmacologic agents and brief open-chest heart massage. To further examine whether the animals could be resuscitated, each animal was given two additional doses of BUP. This resulted in another CV collapse, and all the animals were resuscitated again after each collapse.

In two of the six animals, the initial 5 mg/kg dose of BUP resulted in sustained runs of ventricular tachycardia. In the remaining four animals, and in all animals on the second and third BUP administrations, the rhythm that developed was a slow idioventricular rhythm with broad QRS complexes and electromechanical dissociation. Without treatment, this rhythm



**Table 2.** Mean Arterial Pressure and Heart Rate after Bupivacaine Overdose and after Resuscitation

Time	Mean arterial pressure (% of control) <sup>a</sup>	Significance from control ( <i>P</i> < 0.05)	Heart rate (% of control) <sup>a</sup>	Significance from control ( <i>P</i> < 0.05)
1st BUP dose	0	S	40 ± 25	S
1st Resuscitation	110 ± 27	NS	87 ± 10	NS
2nd BUP dose	0	S	37 ± 22	S
2nd Resuscitation	90 ± 25	NS	65 ± 20	S
3rd BUP dose	0	S	30 ± 10	S
3rd Resuscitation	95 ± 19	NS	55 ± 19	S

Values are given as mean ± SD. NS, not significant; S, significant.

<sup>a</sup>Before first dose of BUP and before apnea, with a 30-min observation period allowed to establish baseline.

**Table 3.** Bupivacaine Dose and Resuscitation Time

BUP administration	BUP dose (mg/kg)	Difference between doses	Resuscitation time (min)	Difference between doses
First	23.3 ± 16.0	NS <sup>a</sup>	1.4 ± 0.5	NS
Second	25.8 ± 17.4	NS	2.2 ± 1.3	NS
Third	15.0 ± 5.5	NS	3.8 ± 3.3	NS

Values are given as mean ± SD. NS, not significant.

<sup>a</sup>Not statistically significant (*P* > 0.05).

could be expected to progress quickly to asystole. It is interesting that none of the animals developed ventricular fibrillation even after repeated administration of BUP. We anticipated that most drug administrations would result in premature ventricular contractions, ventricular tachycardia, or ventricular fibrillation based on available evidence (1,2,4,5). However, as noted above, only two administrations of BUP resulted in ventricular tachycardia, while the other sixteen resulted in a slow idioventricular rhythm.

The ventricular tachycardia responded to bretylium. Direct current cardioversion was not required for conversion to sinus rhythm. Bretylium was used because it had not been evaluated for local anesthetic arrhythmia treatment and because of several theoretical advantages. First, the mechanism of action of bretylium is different than the more commonly administered antiarrhythmic drug, lidocaine. Lidocaine shortens the ventricular action potential duration and the effective refractory period (9). Bretylium lengthens the duration of the ventricular action potential and the duration of the effective refractory period (10). Bretylium also does not slow conduction, which is an advantage over the conduction disturbances induced by BUP (11). Secondly, bretylium exhibits no central nervous system toxicity (12) unlike lidocaine, which can cause seizures (13). The central nervous system toxicities of BUP and lidocaine are additive (14); therefore, in theory it is possible for another seizure to occur after the administration of lidocaine. In our two cases of sustained ventricular tachycardia, bretylium restored sinus rhythm. We chose the dose of 30 mg/kg because this represents the upper range of the clinical dose (12).

The most common ECG tracing was a slow idioventricular rhythm with broad QRS complexes and resultant electromechanical dissociation. This rhythm is similar to the one described by Thigpen et al. (4).

All sixteen dogs in which this rhythm developed during our study were resuscitated with the use of epinephrine, atropine, and open-chest massage. Bicarbonate was administered if the arterial pH indicated the presence of metabolic acidosis. The doses of these drugs are shown in Table 4. On the basis of weight, these drugs were given in amounts larger than the usual clinical doses. For example, the mean dose of epinephrine was 0.92 mg for the first resuscitation or 44.0 µg/kg in our animals. A dose of one mg of epinephrine in a 70-kg human would be 14.3 µg/kg. Epinephrine was selected for its effects on inotropic, dromotropic, and chronotropic properties (15). Atropine was selected for its positive chronotropic effects. We did not attempt to establish a dose-response relationship with these drugs or to evaluate which agent is superior for resuscitation. The intent was to use both drugs together to establish that the CV toxicity of BUP could be treated. In all the animals, epinephrine and atropine rapidly brought a return to baseline blood pressure.

It is possible that hypoxia and acidosis may aggravate the CV toxicity of BUP (1,4). This is important because patients may experience a grand mal seizure and quickly become acidotic and hypoxic after an accidental intravenous injection of BUP. We attempted to reproduce the respiratory effects of a seizure by making the animals apneic for 90 sec at the start of the first BUP injection. After the 90-sec period of apnea, the animals were ventilated with 100% oxygen. This experimental method is similar to the clinical situation during a seizure when the patient becomes apneic or is difficult to ventilate for 1–2 min and then is ventilated with 100% oxygen.

The animals were severely hypoxic at the end of the 90 sec of apnea. None of the animals in the control period sustained arrhythmias other than sinus bradycardia and all became hypertensive. However, during the period of apnea after BUP administration, blood pressure decreased in all animals. Some animals did not sustain complete CV collapse until after several more doses of 5 mg/kg BUP were given after ventilation with 100% oxygen.

Table 4. Total Amounts of Drugs Given during Resuscitation

BUP administration	Epinephrine (mg)	Difference between doses	Atropine (mg)	Difference between doses	Bicarbonate (mEq)	Difference between doses
First	0.92 ± 0.74	NS <sup>a</sup>	1.0 ± 1.1	NS	33.0 ± 25.8	NS
Second	1.16 ± 0.93	NS	1.67 ± 1.75	NS	8.3 ± 20.4	NS
Third	1.42 ± 0.97	NS	2.25 ± 1.17	NS	28.0 ± 31.3	NS

Amounts given as mean ± SD.

<sup>a</sup>NS, not statistically significant ( $P < 0.05$ ).

It was not feasible to allow these animals to remain apneic longer than 90 sec because the resulting severe degree of hypoxia would have precluded meaningful interpretation of the data after resuscitation. In spite of the hypoxia induced, all the animals could be resuscitated after the CV toxic dose of BUP.

The dose of BUP required to produce CV collapse in the first administration period averaged  $23.3 \pm 16.0$  mg/kg. The second and third doses ( $25.8 \pm 17.4$  mg/kg and  $15.0 \pm 5.5$  mg/kg, respectively) were each given after the animal had been stable for 5 min without need for additional pharmacologic support. The total dose given was  $64.1 \pm 26.8$  mg/kg given over  $41.4 \pm 10.2$  min. After each resuscitation, the blood pressure returned to baseline levels, but after the second and third resuscitations the heart rate was only  $65\% \pm 20\%$  and  $55\% \pm 19\%$  of control, respectively. The ECG usually showed sinus rhythm with broad QRS complexes, indicating a conduction disturbance was still present. These data indicate that the cardiac effects of BUP had not completely abated when the second and third doses of BUP were given. In spite of this persistent drug effect, the animals could be resuscitated each time. The mean time for the third resuscitation was  $3.8 \pm 3.3$  min, which is longer than the first, but not statistically significant. All animals had stable blood pressure for at least 15 min after the last resuscitation without need for additional pharmacologic support.

All of the animals required a 1- to 2-min period of open-chest heart massage after the BUP-induced CV collapse to allow for circulation of the resuscitative drugs. We chose open-chest massage because of the configuration of the animal chest wall. Unlike the human chest with a flat sternum that allows for easy anterior to posterior compression, the animal sternum is thicker, rounded, and does not allow for as effective anterior to posterior compression. Open-chest heart massage allows for consistency of cardiac resuscitation and eliminates the variable of attempting to compress the chest wall. At the start of the project, we anticipated that prolonged heart massage would be required as indicated by the available evidence (1,2,4,6). However, the time required was quite brief, usually

only 1-2 min, to allow circulation of the drugs administered.

The fluid requirements in our animals were dictated by operative blood loss, creation of a surgical third space, and hemodynamic changes associated with BUP. Fluids were given in amounts adequate to maintain right atrial pressure between 4 and 10 mm Hg, the average fluid replacement being  $104 \pm 42$  ml·kg<sup>-1</sup>·hr<sup>-1</sup>. It is probable that had we not monitored the right atrial pressure constantly, we would not have given the volume required. The success of our resuscitation would probably have been diminished if our animals were allowed to become hypovolemic.

Others have also studied the CV toxicity. Avery et al. (16), for example, did so in normokalemic and hyperkalemic dogs anesthetized with morphine and nitrous oxide. They administered BUP at a rate of  $0.5$  mg·kg<sup>-1</sup>·min<sup>-1</sup> until fatal CV toxicity occurred. In the normokalemic animals, CV toxicity was reached at a dose of 21.1 mg/kg. They did not attempt to resuscitate their animals. Liu et al. (3) examined the CV toxicity of amide local anesthetics in dogs anesthetized with 30 mg/kg pentobarbital and ventilated with oxygen-enriched room air. They found that the single dose LD<sub>50</sub> of BUP was 11 mg/kg and the cumulative LD<sub>50</sub> was 20.4 mg/kg. In their animals, death resulted from hypotension, bradycardia, and finally, cardiac asystole. Ventricular tachyarrhythmias occurred in none of their animals, and no attempt was made to resuscitate the animals once cardiac toxicity had occurred. Sage et al. (17) examined the CV effects of BUP in awake dogs given a convulsive dose of BUP (3.4 mg/kg) or 1.5 times this dose intravenously over 30 sec. Two of the seven animals given BUP developed ventricular tachycardia and died; the other five had no ventricular arrhythmias. They did not attempt to resuscitate the animals. They concluded that in some awake dogs, BUP may result in ventricular arrhythmias.

The CV toxic dose of BUP during the first administration of the drug in our study averaged 23.3 mg/kg. This is similar to the 21.2 mg/kg found by Avery et al. (16), but is larger than the 11.0 mg/kg found by Liu et al. (3). This difference could be due to use of

different anesthetics (morphine and ketamine vs pentobarbital), but more likely it was due to differences in the rate of administration of intravenous BUP. We administered BUP at a rate of 5 mg/kg over 10 sec every minute (i.e., 23.3 mg/kg over 4.7 min). Avery et al. (16) used a dose of 21.1 mg/kg over a period of 42 min. Thus in our study and in that of Avery et al., BUP was administered more slowly than the rate used by Liu et al. (3) (an 11 mg/kg bolus dose after a 3 mg/kg dose). The rapid administration of BUP by Liu et al. (3) caused a higher peak plasma BUP level and thus a greater likelihood of toxicity.

Ventricular tachycardia was produced by BUP in only two of our anesthetized dogs; the dose that produced the tachycardia was 5 mg/kg. This is only slightly greater than the 3.4 mg/kg that caused ventricular tachycardia in two of the awake animals studied by Sage et al. (17). It is apparent that although some dogs will develop ventricular tachyarrhythmias at these low doses (and presumably lower plasma concentrations) of BUP, most will not develop ventricular tachyarrhythmias even with higher doses but instead will develop hypotension, conduction blocks, and finally electromechanical dissociation. The above reports, along with our study, suggest that whether experimental animals are anesthetized does not appear to affect the incidence of ventricular tachyarrhythmias. It is not clear why some of these animals developed tachyarrhythmias while most others did not.

Thigpen et al. (4) examined the cardiac effects of BUP in hypoxic acidotic sheep. They found that after 4.2 mg/kg BUP given over 10 sec, all animals experienced cardiovascular collapse. Despite pharmacologic therapy, chest compression for at least 20 min, and correction of the hypoxia and acidosis, none of the animals could be resuscitated. Their results contrast the results in our animals. The dose we used was much higher (23.3 mg/kg for the first administration in dogs vs 4.2 mg/kg in sheep), so it would appear that the amount and rapidity of administration could not account for the difference in survival between the animals in the two different studies. The degree of hypoxia in our animals was also greater than that in the sheep studied by Thigpen et al. (4). The  $\text{PaO}_2$  in our dogs was 22 mm Hg after apnea, while the mean  $\text{PaO}_2$  of the sheep was 50 mm Hg. Acidosis was greater (pHa 7.15) in the sheep used by Thigpen et al. (4) than in our dogs (pHa 7.35). It seems unlikely that the degree of acidosis could account for the difference in survival between the two investigations. It is possible that a true species difference could exist between the dog and sheep with regard to BUP sensitivity.

The success of our resuscitation efforts can be at-

tributed to the following factors: the use of bretylium for ventricular tachyarrhythmias possessed several theoretical advantages as outlined earlier in the text; the use of larger than usual doses of epinephrine and atropine during resuscitation; the prevention of hypovolemia by constant monitoring of right atrial pressure; the open-chest heart compression assured good perfusion and circulation of administered resuscitative drugs; the possible protective effects on the sympathetic nervous system stimulation associated with ketamine anesthesia (18); and the possible species differences between sheep and dogs, with sheep being more sensitive to BUP.

In summary, this study demonstrates that anesthetized dogs given repeated CV toxic doses of BUP can be resuscitated. Future studies of BUP CV toxicity and resuscitation should examine further not only the usefulness of bretylium as an alternative to lidocaine for treatment of ventricular tachyarrhythmias, but also the use of larger doses of epinephrine and atropine to treat bradycardia and electromechanical dissociation. The possibility of species differences between sheep and dog emphasizes the need for caution in attempting to extrapolate results of our animal studies to humans.

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## Fentanyl Does Not Inhibit Fertilization or Early Development of Sea Urchin Eggs

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BRUCE DL, HINKLEY R, NORMAN PF. Fentanyl does not inhibit fertilization or early development of sea urchin eggs. *Anesth Analg* 1985;64:498-500.

*Sea urchin (Lytechinus variegatus) eggs have been used to study the effects of fentanyl on in vitro fertilization and early development as a model of human in vitro fertilization. Fentanyl did not affect fertilization or subsequent cell division when present in concentrations calculated to approximate or exceed those to which human ova would be*

*exposed during clinical anesthesia. Lytechinus eggs exposed to fentanyl, then washed in fentanyl-free sea water before fertilization were also not affected and divided normally. The results suggest potential clinical utility of fentanyl during the harvesting of human ova for subsequent in vitro fertilization.*

Key Words: ANESTHETICS, INTRAVENOUS—fentanyl. BIOLOGY—fertilization.

The recent advent of in vitro fertilization of human ova has prompted consideration of any possible effect of anesthetic drugs on this process. When choosing the agents to facilitate laparoscopic harvesting of ova, it is essential to rule out adverse effects of these drugs on subsequent in vitro fertilization. A secondary consideration is that these patients are ambulatory. Anesthesia should be readily reversible to facilitate their returning home. A very popular technique to achieve this goal relies on intravenous fentanyl as the primary anesthetic. Because this drug is highly fat soluble, it might enter the ova to be harvested. Also an adverse action of morphine on in vitro fertilization of the sea urchin egg was demonstrated in 1976 (1). We, therefore, used this model system to study the effect of fentanyl.

### Methods

Gametes of the sea urchin *Lytechinus variegatus* were collected by routine methods. Sperm was obtained by excising testes from the body cavity, blotting on filter paper, and then placing in Syracuse dishes on ice until used. Eggs were collected by KCl-induced spawning. Artificial sea water (SW) containing 5 mM TAPS buffer

(tris(hydroxymethyl) methylamino propane sulfonic acid), pH 8.3, was used in all experiments.

The effects of fentanyl on fertilization and development of echinoderm eggs were studied in two ways. First, fentanyl was added to SW-TAPS to give a final concentration of either 3.3 or 33 nM. Eggs were then suspended in the fentanyl-containing SW for 1 hr, collected by gentle centrifugation, and washed twice in 5 ml of fentanyl-free SW. The eggs were then suspended in 20 ml SW at a concentration of  $2 \times 10^5$  cells/ml (determined volumetrically). To fertilize the eggs, stock sperm suspensions were prepared by diluting 5  $\mu$ l sperm with 40 ml SW. The sperm concentration in the stock suspension was determined by hemacytometry to be about  $2 \times 10^7$  cells/ml. Thus the sperm/egg ratio in all experiments was about 100:1. Previous experiments showed that this ratio routinely caused less than 7-10% polyspermic cells. The SW in the vial overlying the settled eggs was aspirated and 20 ml of sperm suspension was added with gentle swirling. To determine whether fentanyl had any effect on the elevation of the fertilization membrane (slow block to polyspermy), 1-ml aliquots of the fertilized eggs were removed at 30-sec intervals beginning immediately after fertilization and fixed in an equal volume of 5.6% formaldehyde in SW-TAPS, pH 8.0. The percent of eggs possessing complete fertilization membranes was determined by light microscopy. The remainder of the eggs were distributed between two petri dishes and allowed to develop. One dish was fixed with formaldehyde at the end of the first cleavage (65 min). The percentages of normally and abnormally developing cells were determined, as

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Table 1. Percent Eggs with Complete Fertilization Membranes

Treatment	Time after fertilization			
	0 sec	30 sec	60 sec	90 sec
3.3 nM fentanyl (preexposure)	12	41	94	99
Control	15	39	95	99
33 nM fentanyl (preexposure)	8	18	95	100
Control	10	40	95	99
66 nM fentanyl (at fertilization)	9	39	95	99
Control	11	45	96	100

At least 100 cells were counted at each time point.

well as the percentage of cells failing to divide. Abnormally dividing eggs were defined as embryos having an unequal number of blastomeres or blastomeres of different size. The eggs in the other dish were allowed to develop into free-swimming pluteal larvae. Eggs not preexposed to fentanyl were fertilized at the same sperm/egg ratio and used as controls.

In the second experiment eggs were diluted to  $2 \times 10^5/\text{ml}$  in SW containing 66 nM of fentanyl and fertilized as described above with sperm that was also diluted in SW containing 66 nM of fentanyl. The effects of fentanyl on fertilization membrane formation, the percent cells undergoing abnormal cleavage, and on development to the pluteal larva stage were examined as described above. Controls were fertilized in the absence of fentanyl.

## Results

The effect of fentanyl on the percentage of cells with complete fertilization membranes is shown in Table 1. We could find no consistent evidence that fentanyl delayed or prevented fertilization membrane formation (structural block to polyspermy). Table 2 summarizes the effect of fentanyl on the development of echinoderm eggs through the first cell division. There were no significant differences in the number of cells undergoing abnormal development whether eggs were preexposed to fentanyl or fertilized in the presence of the drug. The abnormally dividing cells seen in each experiment were due to polyspermy (determined by orcein staining methods) and were expected to occur at the frequencies seen in the controls, at the sperm/egg ratio used. Cultures examined after 24 hr revealed no detectable differences in the number of cells successfully completing development to the pluteal larva stage.

Table 2. Effect of Fentanyl on Development through the First Cell Division

Treatment	Normal	Percent abnormal	Undivided
3.3 nM fentanyl (preexposure)	90	7	3
Control	89	9	2
33 nM fentanyl (preexposure)	91	8	1
Control	89	8	3
66 nM fentanyl (at fertilization)	91	7	2
Control	92	6	2

All cells fixed at the end of the first cell cleavage (65 minutes). At least 300 cells were counted for each experimental and control group in each experiment.

## Discussion

Sea urchins (*Arbacia*, *Lytechinus*) are members of the class Echinoidea that reproduce by shedding sperm and eggs into sea water, where fertilization takes place (2). After fertilization, cell division is rapid and a free-swimming, ciliated blastula results within the ensuing 12 hr. Because this process is normally in vitro and is easily visible, it is a good morphological model of human in vitro fertilization. Like human fertilization, one ovum is fertilized by one spermatocyte and multiple sperm entries (polyspermy) is abnormal. Echinoderm eggs may or may not be an equally good pharmacologic model of opiate action, because neither pharmacokinetics (affinity, uptake) nor pharmacodynamics (effect on mitosis and cleavage) of opiates has been definitively examined in these cells. The report that prompted this study suggested that echinoderm fertilization was sensitive to opiates (1).

The choice of fentanyl dose was made according to a series of reasonable assumptions concerning the range of human ova exposure during clinical anesthesia. If a 60-kg woman were given 10 ml of fentanyl (0.05 mg/ml), a somewhat large dose of this drug, she would receive 500  $\mu\text{g}$  of fentanyl citrate, almost exactly 1.0  $\mu\text{M}$ . The volume of distribution ( $V_{dss}$ ) of this drug has been reported as 3.2 (3) and 3.7 (4) L/kg, so an average of 3.5 L/kg would give a  $V_{dss}$  of 210 L in a 60-kg patient. One  $\mu\text{M}$  in 210 L equals 4.8 nM/L. Our doses of 3.3, 33, and 66 nM/L thus span this calculated concentration as well as concentrations of 7 and 14 times greater.

The pH of the sea water in these experiments was 8.3. Because this is higher than the pKa for fentanyl, 7.34 (5), the proportion of fentanyl found as the active, free base would be about 90%. In the body, at pH 7.4, it is by contrast about 50% in free-base form, and



protein binding decreases its activity even further. There was no protein in our artificial sea water. Thus our experiments probably tested active drug concentrations higher than those calculated upon the assumptions listed above. These physical chemical considerations strengthen the conclusion that the results were negative.

An attempt was also made to mimic the two conditions under which human ova would be exposed to fentanyl. The first of these would be extracellular fluid (ECF) containing initial concentrations corresponding to those calculated for dose and  $V_{dss}$ . The second, ex vivo following laparoscopic harvest, would be the tissue culture media solutions in which the harvested ova are suspended. Current clinical practice is to wash, then suspend and fertilize ova in two successive, small aliquots of medium (6). Our wash solutions of fentanyl-free sea water corresponded to these steps. Inhibition of fertilization and subsequent cell divisions was not found either when fentanyl was present or when the *Lytechinus* eggs had been washed after fertilization.

This negative study of fentanyl effect on in vitro fertilization differed from the report of morphine inhibition (1). In those studies, Cardasis and Schuel used morphine sulfate in exposures of  $10^{-3}$ ,  $10^{-5}$ , and  $10^{-7}$  M. Assuming fentanyl to be 100 times as potent as morphine, a comparison of doses of these drugs can be made. The 60-kg patient, given 50 mg of morphine sulfate instead of 0.5 mg of fentanyl, would receive 66  $\mu$ M of morphine. This would be distributed in a  $V_{dss}$  essentially the same as that for fentanyl, 210 L. The ECF concentration would thus be 314 nM/L. Exposures to  $10^{-3}$ ,  $10^{-5}$ , and  $10^{-7}$  M morphine sulfate equal those to  $10^6$ ,  $10^4$ , and  $10^2$  nM/L, respectively, so the calculated concentration of 314 falls between the two most dilute exposures in that experiment. In that range, between 26 and 33% *Arbacia* eggs showed

polyspermy when fertilized in the presence of morphine (1). No such effect was found with fentanyl.

The experimental conditions of the previous morphine study differed from the present one in a way that suggests an alternative explanation to differences in drug action. In the morphine studies, Cardasis and Schuel added one drop of sea water containing 4% (vol/vol) sperm to "2 ml unfertilized" eggs. This appears to be a much greater ratio of sperm to eggs than was used in the present experiments, and in our experience a mass action effect of sperm excess can cause polyspermy. Those workers did, however, report normal controls, so this explanation may not be relevant to their results. Their method is widely used and well accepted by cell biologists working in this field.

The failure of fentanyl to affect fertilization of sea urchin eggs may not be applicable to clinical medicine. Further studies would be required to show a similar, negative effect on human ova.

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## In Vitro Study of the Effect of Epidural Blood Patch on Leakage through a Dural Puncture

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ROSENBERG PH, HEAVNER JE. In vitro study of the effect of epidural blood patch on leakage through a dural puncture. *Anesth Analg* 1985;64:501-4.

*Pressure resistance of an experimental epidural blood patch was studied in vitro. Pieces of canine lumbar dura were perforated with a 19-gauge needle ( $n = 12$ ) or a 25-gauge needle ( $n = 6$ ) and kept between the intercommunicating chambers of a plexiglass apparatus. One chamber (epidural side) was filled with autologous blood and the other chamber (subdural side) was filled with autologous cerebrospinal fluid. Control studies consisted of dural specimens not exposed to blood on the epidural side (19-gauge,  $n = 8$ ; 25-gauge,  $n = 4$ ). After 30 min, the dura was removed and placed in saline for inspection. In blood-treated specimens small sheets of coagulated blood were found attached to the epidural side of the dura, and in eight of the twelve of 19-gauge puncture experiments and one of the six of the 25-gauge puncture experiments clotted blood was visible on the subdural side.*

*The dura was then placed back into the chamber for pressure testing 30 min or 16-18 hr later. The subdural chamber was filled with saline and air was left in the epidural chamber. Pressure (1.5, 20, 30, 40, and 50 mm Hg) was applied by injecting additional saline into the subdural chamber. Each pressure level was maintained for 5 min. Saline leaked through the perforation in all control specimens at 1.5 mm Hg pressure. Four blood-treated specimens showed some leakage at 20 mm Hg. All dura specimens perforated with a 19-gauge needle leaked at 40 mm Hg, five of them only at the lowest score rate, 1-4 drops/5 min. One blood-patched dura perforated with a 25-gauge needle did not leak until the pressure reached 50 mm Hg. The clots remained adherent to the dura throughout the pressure testing. This study suggests that an epidural blood patch applied after puncture of the dura can withstand normal lumbar cerebrospinal fluid pressures in patients in the sitting position.*

**Key Words:** ANESTHETIC TECHNIQUES—epidural.

The epidural blood patch (EBP) is a popular treatment for persisting post-lumbar puncture headache, despite awareness that the procedure may produce neurological complications (1-5) including subdural hematoma (6). Injected autologous blood clots in the epidural space, presumably forming a gelatinous tamponade that prevents the leakage of cerebrospinal fluid (CSF) (7). In an autopsy of an obstetric patient who died from bilateral intracranial subdural hematoma after a lumbar dural tap, a 2-day-old EBP was found to consist of clots adherent to the dura in the lumbar and sacral areas (8).

Because most treated patients are able to sit without getting a headache soon after the epidural injection,

the epidural blood clot apparently resists pressure of at least 11-36 mm Hg, a transdural pressure gradient range observed in patients given spinal anesthesia (9) (assuming that epidural pressure is zero or slightly negative (10)). However, how a blood patch develops and its effectiveness in withstanding various CSF pressures have not been documented. In this study with canine dura we produced an experimental EBP and tested its ability to seal dural puncture sites.

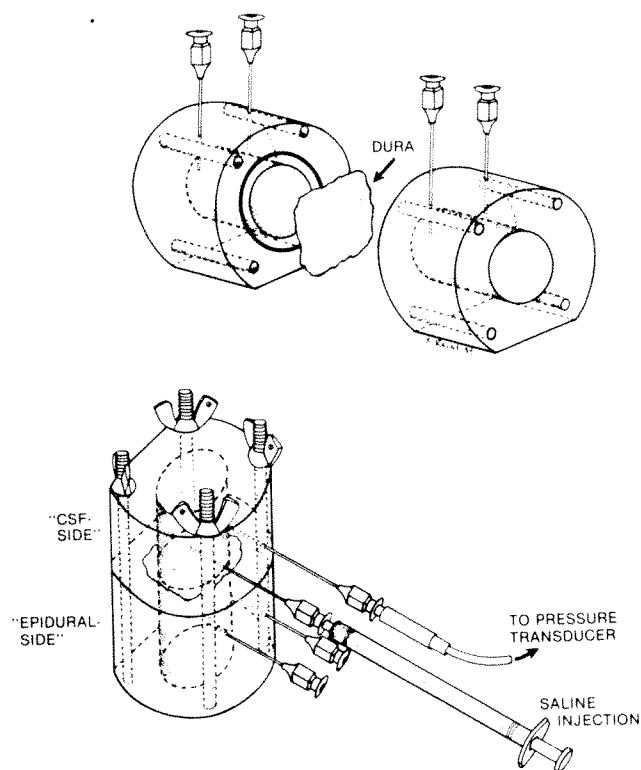
### Materials and Methods

A plexiglass apparatus (Fig. 1) with two intercommunicating chambers (11) was used to study the efficacy of EBP in vitro. Pieces of lumbar dura were carefully dissected from anesthetized dogs. Epidural fat and blood were removed and the dura was perforated with one passage of a 19-gauge ( $n = 12$ ) or 25-gauge ( $n = 6$ ) needle. The dura was then placed over the port of one of the two 10-ml chamber blocks. The other block, containing an identical chamber, was screwed tightly into place with four locating screws. One chamber, the CSF side of the dura, was filled

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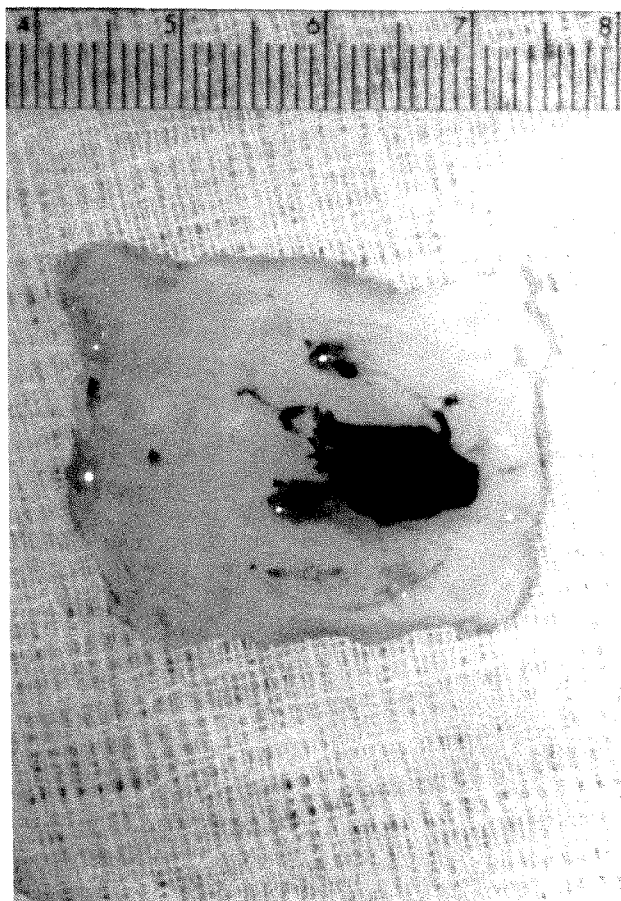
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**Figure 1.** Upper picture: schematic drawing of the apparatus used in the experiments. The dura was placed between the ports of the two chambers for treatment with blood and CSF. Lower picture: the resistance of the blood patches to changes in pressure was tested by leaving the epidural side of the chamber empty while filling the CSF side of the chamber with saline and gradually increasing pressure on the CSF side by additional injections of saline.

with fresh CSF drawn from the cisterna magna of the dog from which the dura was removed; and the other chamber, the epidural side, was simultaneously filled with freshly drawn autologous blood. After 30 min, the dura was carefully dismantled and placed in saline for 30 min (19-gauge,  $n = 6$ ; 25-gauge,  $n = 6$ ), or 16–18 hr (19-gauge,  $n = 6$ ), prior to pressure testing. Pressure testing consisted of remounting the dural sample onto the communicating port of the same two-chamber apparatus with the epidural side left empty except for air at ambient barometric pressure and with the CSF side of the chamber slowly filled with saline. The apparatus was placed with the "CSF chamber" uppermost, separated from the empty "epidural chamber" by the patched dura. Changes in pressure in the "CSF chamber" were induced by injecting saline with a syringe with each pressure level being maintained for 5 min, the pressure being recorded from one of the two inlets of the "CSF chamber" (Fig. 1) using a Statham pressure transducer and a Grass Model 7D Polygraph. The pressures tested were 1.5, 20, 30, 40, and 50 mm Hg (the last one only in dural



**Figure 2.** Photograph of the epidural surface of a piece of lumbar dura following puncture with a 19-gauge needle and then treatment of the epidural side with autologous blood. The photograph was taken approximately 1 hr after conclusion of blood treatment and pressure testing. A sheet of clotted blood remains adherent to dura around the puncture site.

samples perforates with a 25-gauge needle). The leakage of saline through the puncture was scored as – (no dripping of saline into the empty "epidural chamber"), + (1–4 drops/5 min), ++ (5–9 drops/5 min), or +++ ( $\geq 10$  drops/5 min). Controls consisted of pieces of lumbar dura punctured with a 19-gauge ( $n = 6$ ) or 25-gauge needle ( $n = 4$ ), without being treated with blood. Each piece of dura was used for only one experiment. Experiments were done at room temperature.

## Results

Clotted blood became adherent to the dura and formed thin clot sheets of variable sizes on and in the vicinity of the hole in the dura (Fig. 2) while the dura was in the apparatus with blood and CSF. A short band of clotted blood protruded from the hole on the CSF side of the dura in eight of the twelve 19-gauge puncture experiments and in one of the six 25-gauge puncture



experiments. In all control dura samples punctured either with a 19-gauge or a 25-gauge needle there was a marked leak (+ + or more) at the lowest pressure tested (1.5 mm Hg). Pressure could not be increased above 1.5 mm Hg on the CSF side due to an accelerated leakage of saline at each attempt to raise the pressure. Results from pressure testing of the blood treated duras are shown in Table 1. At 20 mm Hg pressure, a leak was observed in only 4 of 12 dura samples perforated with a 19-gauge needle. At 40 mm Hg pressure all samples perforated with a 19-gauge needle were leaking to varying degree, five of them at only the lowest score rate (+). The mean score of leakage at 40 mm Hg pressure was significantly lower when the perforation of the dura was with the 25-gauge needle than it was when the dura had been perforated with a 19-gauge needle ( $P < 0.05$ ). In one of the six experiments with a 25-gauge needle, a minor leak through the patch was detected but only at 50 mm Hg. The sheets of clotted blood remained attached to the dura throughout the study, even when the storage time before pressure testing was 16–18 hr.

## Discussion

The results indicate that an EBP of a 25-gauge needle hole in the dura may resist pressure as high as 40 mm Hg. This pressure is greater than that expected to develop in the subarachnoid space, on the average, when a patient is sitting. An EBP of a puncture made by a 19-gauge needle was somewhat less efficient but resisted pressure up to 30 mm Hg in five of twelve experiments. Epidurally injected saline (10–20 ml) in humans in lateral recumbency causes a transient increase in pressure in both the subarachnoid and the epidural space. The increase lasts from 3 to 10 min (10). Although the CSF pressure peaks at approximately 64 mm Hg (850 mm H<sub>2</sub>O) within a few minutes, the pressure gradient between the subarachnoid space and the epidural space does not exceed 15 mm Hg. After injection of fluid into the epidural space, the pressure gradient may be initially reversed (10). In fact, injected blood could actually enter the hole in the dura and instead of a superficial patch, a clot plug may form. Such a clot plug developed in half of our experiments where the clot was macroscopically visible on the CSF side of the dura after CSF and blood were injected at an assumed identical rate (injection pressure) into their respective chambers.

It is possible that injury of the endothelial like dural membrane promotes coagulation by mechanisms similar to those associated with vascular injuries. Platelet aggregation and adherence are known to be initiated by the presence of collagen (12), which is the main

Table 1. Effect of Pressure in the CSF Chamber on Leakage of Saline through a Hole in the Dura That Has Been Sealed with an Experimental Blood Patch<sup>a</sup>

Experiment no.	Pressure in the CSF chamber (mm Hg)				
	1.5	20	30	40	50
19-gauge hole, 1 hr					
1	—	—	<sup>b</sup>	+++	
2	—	—	—	+	
3	—	+	+	+++	
4	—	—	—	+	
5	—	—	+	+	
6	—	+	++	++	
19-gauge hole, 16.5–18.5 hr					
7	—	—	—	++	
8	—	—	—	+	
9	—	++	+++		
10	—	++	+++		
11	—	—	—	+	
12	—	—	+	+++	
25-gauge hole, 1 hr					
13	—	—	—	—	+
14	—	—	+	+	+
15	—	—	—	+	+
16	—	—	+	+	+
17	—	—	+	+	+
18	—	—	—	++	+++

<sup>a</sup>Pressure testing 1 or 16.5–18.5 hr after blood injection: —, no dripping; +, 1–4 drops/5 min; ++, 5–9 drops/5 min; +++, ≥ 10 drops/5 min.

<sup>b</sup>Not tested.

structural component of the dura (13). After formation, the clot seems to remain quite adherent to the dural surface as observed in our 16–18 hr experiments. As shown in EBP studies in goats, immature fibroblasts start to infiltrate the clot after 1–4 days, and the fibroblastic reaction seems to reach its peak in about three weeks (7), finalizing the healing process.

In summary, results of this in vitro study suggest that the efficacy and high success rate (2) of treatment of post-spinal puncture headache with an epidural injection of autologous blood are due to the formation of an adherent, coagulated EBP.

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## The Effect of Verapamil and EGTA on the Rat Phrenic Nerve-Hemidiaphragm Preparation

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BIKHAZI GB, FLORES C, FOLDES FF. The effect of verapamil and EGTA on the rat phrenic nerve-hemidiaphragm preparation. *Anesth Analg* 1985;64:505-8.

*Relatively high concentrations of verapamil or EGTA [ethylene glycol-bis ( $\beta$ -aminoethyl ether) N, N, N', N'-tetraacetic acid] inhibit contraction (P) of the rat phrenic nerve-hemidiaphragm preparation elicited by direct or indirect stimulation. The inhibitory effect of verapamil is greater ( $P < 0.002$ ) with direct ( $I_{50} = 26.3 \pm 1.7 \mu\text{M}$ ) than indirect ( $I_{50} = 37.6 \pm 1.9 \mu\text{M}$ ) stimulation. For EGTA the reverse is true:  $I_{50}$  is  $1320 \pm 80 \mu\text{M}$  with direct and  $1100 \pm 60 \mu\text{M}$  with indirect stimulation. The greater than*

*90% verapamil-induced depression of P can only be partially reversed by washout. Increasing the  $[\text{Ca}^{2+}]$  or the addition of 4-aminopyridine (4AP) has insignificant antagonist effect. Except for the antagonism by 4AP during direct stimulation, the EGTA-induced depression of P is better antagonized by washout, increase of the  $[\text{Ca}^{2+}]$ , or the addition of 4AP than that caused by verapamil. Neostigmine did not antagonize the depression of P caused by either verapamil or EGTA. The findings presented indicate that the primary site of action of verapamil is postjunctional and that of EGTA is prejunctional.*

**Key Words:** PHARMACOLOGY—verapamil. NEUROMUSCULAR TRANSMISSION—verapamil, EGTA

Appropriate concentrations of extra- and intracellular  $\text{Ca}^{2+}$  is essential for physiological myoneural activity. Thus  $\text{Ca}^{2+}$  is essential for the release of acetylcholine (ACh) by endogenous or exogenous nerve impulse from the motor nerve terminal (1-3), for the stabilization of the pre- and postjunctional membrane (4), initiation of the excitation-contraction coupling (5,6), and the contraction of the muscle fiber (7). The source of  $\text{Ca}^{2+}$  involved in these processes is either extracellular (e.g., extracellular fluid) or intracellular (e.g., sarcoplasmic reticulum, mitochondria) (8,9). The extracellular  $\text{Ca}^{2+}$  is called "trigger  $\text{Ca}^{2+}$ " and the intracellular  $\text{Ca}^{2+}$ , which is ultimately responsible for the effect of  $\text{Ca}^{2+}$ , is referred to as "activator  $\text{Ca}^{2+}$ " (9,10). Compounds such as 4-aminopyridine (4AP) that increase (11) the intracellular influx of  $\text{Ca}^{2+}$  or the release of  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum (12) and from other intracellular structures, facilitate neuromuscular (NM) transmission and muscle contraction. Compounds that limit the diffusion of  $\text{Ca}^{2+}$

through membranes (e.g., manganese, lanthanum, local anesthetics, barbiturates, morphine, methadone, alcohol, neomycin, prenylamine derivatives, and many others (9,13)) inhibit muscular contraction. Of these, the pharmacology of the prenylamine group has been investigated most extensively. Some of these compounds (e.g., verapamil, nifedipine, diltiazem) are widely used for the treatment of cardiovascular disorders (14,15).

The precise mechanism of action of the prenylamine type Ca-channel blockers is still subject of debate (16). It is believed that there are at least two types of channels through which  $\text{Ca}^{2+}$  can enter the cell interior. One of these depends on the membrane potential and is activated by membrane depolarization. The other is activated through specific receptors independent of membrane potential (see (16)). The prenylamine type Ca-channel blockers primarily act on the potential-dependent channels and inhibit the "slow" inward  $\text{Ca}^{2+}$  current (16,17). Verapamil (18,19) and diltiazem (20) also block the "fast"  $\text{Na}^+$ -channels through which  $\text{Ca}^{2+}$  can also enter the cell interior (21,22). In contrast, nifedipine selectively blocks the slow Ca-channels (23).

The pharmacological effects of Ca-channel blockers have been investigated extensively on the heart, vascular, respiratory and intestinal smooth muscle, frog, crayfish, and barnacle muscle, and on the stimulus-excretion coupling of endocrine and exocrine glands

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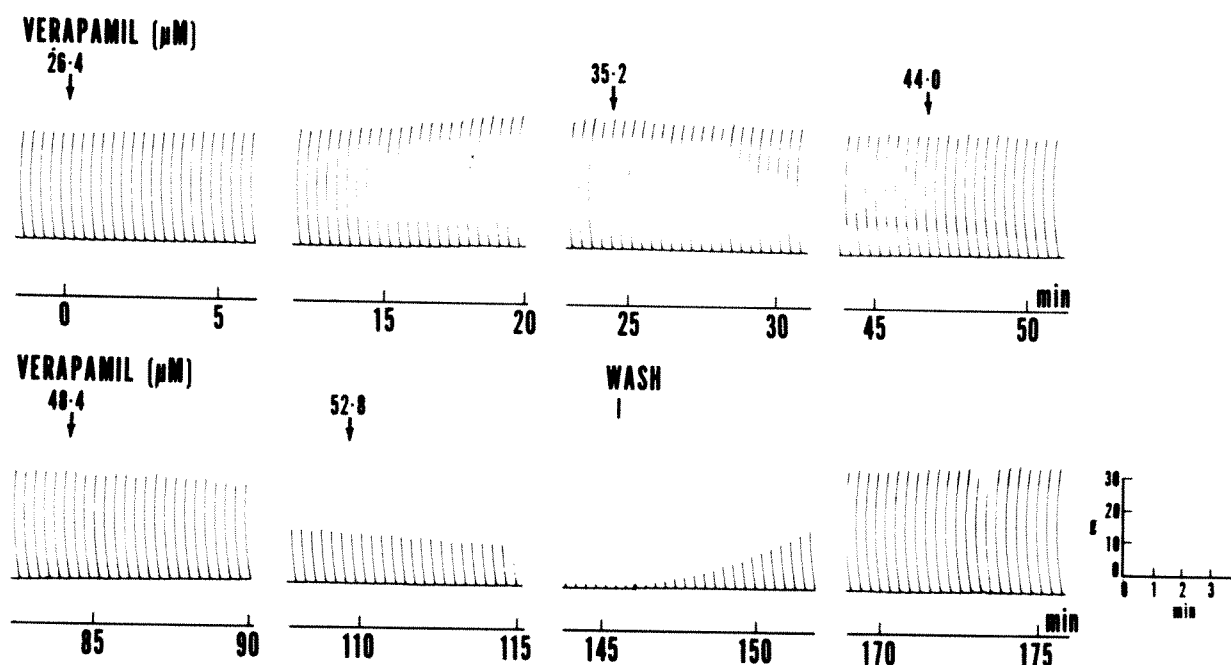


Figure 1. The myoneural effect of verapamil on the indirectly stimulated rat phrenic nerve-hemidiaphragm preparation. Note that verapamil, before inhibiting, increased twitch tension.

(see (9) and 24)). Despite the important role of  $\text{Ca}^{2+}$  in NM transmission and muscular contraction, little information is available on the effect of Ca-channel blockers on mammalian myoneural activity (25).

In this study, the myoneural effects of verapamil and EGTA [ethylene glycol-bis ( $\beta$ -aminoethyl ether) N,N,N',N'-tetra acetic acid], a calcium chelating agent (26), were observed on the directly or indirectly stimulated rat phrenic nerve-hemidiaphragm preparations. The influence of washout,  $\text{Ca}^{2+}$ , or 4-aminopyridine (4AP) on the myoneural effects of verapamil and EGTA were also observed.

## Methods

Twenty-four male Sprague-Dawley rats of 250–300 g body weight were lightly anesthetized with ethyl ether and decapitated. The phrenic nerves and the diaphragm were dissected, and the phrenic nerve-hemidiaphragm preparations (27) were suspended in specially designed organ baths (28) in modified Krebs' solution containing 1.4 mM  $\text{CaCl}_2$  and 0.9 mM  $\text{MgSO}_4$ . In the presence of these  $[\text{CaCl}_2]$  and  $[\text{MgSO}_4]$  the physiologically important  $[\text{Ca}^{2+}]$  (1.1 mM) and  $[\text{Mg}^{2+}]$  (0.8 mM) is the same as in human or rat plasma (29). The bath was aerated with 95%  $\text{O}_2$ –5%  $\text{CO}_2$  and its temperature was maintained at 37°C. Under these conditions the pH of the bath was between 7.38 and 7.42.

The 48 phrenic nerve-hemidiaphragm preparations were stimulated (Grass Model S48B stimulator) either indirectly through the phrenic nerve, or directly by a pair of needle electrodes inserted about 1-cm apart into the muscle, with 0.1-sec trains of 50-Hz supramaximal impulses administered every 20 sec (30). The stimulus duration was 0.2 msec during indirect and 2.0 msec during direct stimulation. A resting tension of 10 g was applied to the diaphragms. To eliminate the "indirect component" (31) of direct stimulation, NM transmission was blocked with 3  $\mu\text{g}/\text{ml}$  *d*-tubocurarine during direct stimulation. The isometric tension output (P) was quantitated with FT03 transducers and continuously recorded on a Grass Model 70 polygraph.

After the preparations became stable, the cumulative dose-response relationships of verapamil or EGTA were determined in 12 experiments with each compound, during indirect and on 12 others during direct stimulation. The initial concentration of verapamil was 20 nmol/ml (20  $\mu\text{M}$ ) and that of EGTA 1  $\mu\text{mol}/\text{ml}$  (1 mM). The concentration of verapamil was gradually increased at first by 10 nmol/ml and later by 5 nmol/ml until P decreased to less than 10% of control. The increments of EGTA were 0.1  $\mu\text{mol}/\text{ml}$ . The concentrations of verapamil or EGTA were increased whenever P became stable after the previous dose.

The concentrations of verapamil and EGTA required to produce 50 ( $I_{50}$ ) and 90 ( $I_{90}$ )% of inhibition of P were determined from the computer derived log dose-response regression lines. In four experiments each, the effect of washout, or the increase of the

Table 1. The Myoneural Potency of Verapamil and EGTA and Reversibility of the Greater than 90% Myoneural Block Caused by these Compounds

Compound	Stimulation	$I_{50}$ ( $\mu$ M)	$I_{90}$ ( $\mu$ M)	Tension output (% of control) after		
				Washout	CaCl <sub>2</sub> <sup>a</sup>	4AP (40 $\mu$ M)
Verapamil	Indirect	37.6 $\pm$ 1.9 <sup>b</sup>	47.9 $\pm$ 1.9	46.0 $\pm$ 3.9 <sup>c</sup>	12.5 $\pm$ 3.2	19.9 $\pm$ 2.1
	Direct	26.3 $\pm$ 1.7 <sup>c</sup>	39.8 $\pm$ 2.5 <sup>f</sup>	41.0 $\pm$ 2.4	17.5 $\pm$ 1.5	28.0 $\pm$ 3.6
EGTA	Indirect	823.2 $\pm$ 8.6	864.0 $\pm$ 11.5	71.5 $\pm$ 3.8	79.7 $\pm$ 3.7	106.8 $\pm$ 3.6
	Direct	1100.0 $\pm$ 60.0 <sup>c</sup>	1320.0 $\pm$ 80.0 <sup>c</sup>	66.3 $\pm$ 4.6	44.3 $\pm$ 2.4 <sup>d</sup>	28.1 $\pm$ 3.8 <sup>d</sup>

<sup>a</sup>[CaCl<sub>2</sub>] increased from 1.4 to 2.5 mM.<sup>b</sup> $I_{50}$  and  $I_{90}$  values are means  $\pm$  SEM of 12 experiments.<sup>c</sup>Reversal data are means  $\pm$  SEM of four experiments.<sup>d,e,f</sup> and <sup>g</sup> indicate significant difference at the  $P < 0.001$ , 0.002, and 0.05 levels (Student's *t*-test), respectively, between the parameters observed during direct and indirect stimulation.

[CaCl<sub>2</sub>] of the organ bath from 1.4 to 2.5 mM, or the addition of 40  $\mu$ M 4AP on the greater than 90% depression of P by verapamil or EGTA, was evaluated during both indirect and direct stimulation.

The statistical significance of the differences of the potency and the reversibility data during indirect and direct stimulation were determined with Student's *t*-test.

## Results

During indirect stimulation, verapamil initially increased P (Fig. 1). The inhibitory potency of verapamil was greater ( $P < 0.001$ ) during direct than indirect stimulation (Table 1). In contrast, EGTA was more effective ( $P < 0.001$ ) during indirect than direct stimulation (Table 1). The log dose-response regression line of EGTA was very steep.

The greater than 90% depression of P by verapamil or EGTA could be antagonized only partially by washout during either indirect or direct stimulation. Increasing the [CaCl<sub>2</sub>] from 1.4 mM ([Ca<sup>2+</sup>] = 1.1 mM) to 2.5 mM ([Ca<sup>2+</sup>] = 2.0 mM) or adding 40  $\mu$ M 4AP had little antagonist effect on the verapamil induced depression of P during indirect and direct stimulation (Table 1). The EGTA induced depression of P, however, was well antagonized by both Ca<sup>2+</sup> or 4AP during indirect, and moderately during direct, stimulation. Neostigmine methylsulfate, 0.25  $\mu$ M, did not antagonize the depression of P caused by either verapamil or EGTA.

## Discussion

In relatively high concentrations, both verapamil and EGTA inhibited the indirectly or directly evoked contractions of the rat phrenic nerve-diaphragm preparation. The mechanism and the primary site of action of verapamil and EGTA appear to be different. Verapamil interferes with the availability of Ca<sup>2+</sup> by inhibiting its passage through excitable membranes.

EGTA chelates Ca<sup>2+</sup> (26). The finding that the  $I_{50}$  and  $I_{90}$  of verapamil were greater during indirect than during direct stimulation suggests that verapamil may have a facilitating effect on NM transmission. The mechanism of the facilitating effect of verapamil could not be determined under the experimental conditions used. Because ACh is released in 5- to 10-fold excess by the nerve impulse (32), it is unlikely that the facilitating effect of verapamil is due to a further increase of stimulated ACh release. It is conceivable, however, that verapamil antagonizes the stabilizing (antidepolarizing) effect of Ca<sup>2+</sup> on the postjunctional membrane (4). This assumption is supported by the observation that 40  $\mu$ M of verapamil causes approximately 10 mV depolarization of pig muscle fibers (personal communication, Esther Gallant, PhD, College of Veterinary Medicine, University of Minnesota, St. Paul, MN 55108). Facilitation of the depolarization of the postjunctional membrane would increase the voltage of the endplate potential. This in turn could explain why higher concentrations of verapamil were required for the inhibition of the excitation-contraction coupling during indirect stimulation, which is dependent on the endplate potential, than during direct stimulation when muscle contraction is elicited by an external current.

In contrast to the situation with verapamil, NM transmission appears to be more sensitive to the lowering of the [Ca<sup>2+</sup>] due to chelation by EGTA, than the contractile mechanism. Thus the  $I_{50}$  and  $I_{90}$  of EGTA is lower during indirect than during direct stimulation.

Verapamil interferes with the passage of Ca<sup>2+</sup> through excitable membranes. Therefore it is understandable that neither increasing the [Ca<sup>2+</sup>] or attempting to facilitate the intracellular passage of Ca<sup>2+</sup> by 4AP antagonized the effects of verapamil. In contrast, adding more Ca<sup>2+</sup> or facilitating the intracellular utilization of nonchelated Ca<sup>2+</sup> by 4AP antagonized the EGTA-induced depression of P.

EGTA has no therapeutic applications, and con-

centrations of verapamil that would cause significant decrease of myoneural activity are not likely to be encountered under clinical circumstances. Preliminary studies indicate, however, that concentrations of verapamil that may be encountered under clinical circumstances potentiate the effect of NM blocking agents both in vitro (33) and in vivo (34).

Because it is difficult to wash out verapamil, after prolonged administration verapamil may accumulate in the muscle. Therefore the possibility can not be excluded that the accumulation of verapamil in surgical patients, or its intravenous administration during surgery may increase the intensity or prolong the duration of action of NM blocking agents. Indeed, it has been reported (33,35) that the NM block caused by the combination of verapamil and NM blocking agents is difficult to reverse.

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## Effects of Low-Dose Morphine and Fentanyl Infusions on Urinary and Plasma Catecholamine Concentrations during Scoliosis Surgery

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PATHAK KS, ANTON AH, SUTHEIMER CA. Effects of low-dose morphine and fentanyl infusions on urinary and plasma catecholamine concentrations during scoliosis surgery. *Anesth Analg* 1985;64:509-14.

*Plasma and urinary catecholamines were measured in 20 patients during scoliosis surgery to determine whether low dose fentanyl ( $1.5\text{--}2.5\ \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and morphine ( $150\text{--}250\ \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) affect the catecholamine stress response to surgery differently. In all patients epinephrine ( $1.6\text{--}11.4\ \mu\text{g}/\text{kg}$ ) was injected locally at the operative site for hemostasis. This was an advantage because exogenous and endogenous epinephrine undergo the same fate and the*

*increase in epinephrine might enhance otherwise subtle effects. The data indicate that both narcotics have similar effects on catecholamine metabolism but that even low doses of fentanyl are more effective than morphine in obtaining the catecholamine response to painful stimuli. Also, post-operative differences in plasma epinephrine indicate that recovery of awareness, and thus the onset of postoperative pain, is more rapid in patients receiving fentanyl.*

**Key Words:** ANESTHESIA, INTRAVENOUS—opioids. SYMPATHETIC NERVOUS SYSTEM—catecholamines.

Depending on the dose, both morphine and fentanyl can attenuate many of the hormonal responses to the stress of surgery, with fentanyl apparently being more effective at equianalgesic doses (1-6). Surgery-induced activation of the sympathetic nervous system, however, is one of the most resistant stress responses to be modulated by anesthesia, be it narcotic or inhalational (3,6-9). This sympathetic stimulation is manifested by an increase in plasma and urinary catecholamine concentrations (2,10-15).

In a previous study (16) comparing the hemodynamic effects of low dose morphine and fentanyl given by infusion or bolus injections during surgery for scoliosis, we had the clinical impression that hypertension occurred more frequently with morphine. We hypothesized that this probably was due to greater sympathetic nervous activity in the morphine-treated patients. Because a difference in the effects of morphine and fentanyl on catecholamine metabolism and disposition could contribute to their different effects on modulating the response to stress, we compared the effect of the two narcotics on catecholamine metabolism in patients during corrective spinal surgery

for scoliosis. Changes in plasma concentrations of epinephrine and norepinephrine and the urinary levels of these amines and their metabolites were used as a measure of the changes in metabolism and disposition. This model was selected for study because, first, the patient population was relatively young, drug-free, and otherwise healthy; therefore, our results would not be confounded by drugs and cardiovascular or other functional pathology. Second, relatively low doses of narcotics would be used that, especially with morphine, would avoid complicating side effects such as histamine release (17), occasional severe hypotension or hypertension (18), and an increased volume requirement secondary to marked vasodilation (19). Third, the fact that these patients were also receiving epinephrine locally for hemostasis was an advantage because exogenous epinephrine is subject to the same metabolic, physiological, and pharmacological influences as endogenous epinephrine (20,21) and the consequent increase in pool size might enhance otherwise subtle changes.

### Methods

#### *Patients and Preinduction Preparation*

Twenty otherwise healthy (ASA class I) patients with idiopathic scoliosis and no underlying pulmonary disease scheduled for surgery were selected for the study, which was approved by our Institutional Review Board.

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The 20 patients (14 women and 6 men, aged 11–48 yr) were randomly divided into a group receiving morphine and a group receiving fentanyl. All patients were premedicated with intramuscular secobarbital (2 mg/kg) and atropine (0.005 mg/kg) 90 min prior to surgery.

Two intravenous catheters for drugs, fluids, and blood as well as a radial arterial cannula for measurement of blood pressure, blood gas tensions, and blood sampling were inserted in all patients. Monitors included ECG, esophageal temperature probe, esophageal stethoscope, and nerve stimulator. Maintenance fluids were calculated at a rate of  $1.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$  after cessation of oral intake, and 50% of this volume was infused before induction of anesthesia.

### Anesthesia Protocol

After hydration and monitoring, anesthesia was induced with either an initial bolus of morphine (250  $\mu\text{g/kg}$ ) or fentanyl (2.5  $\mu\text{g/kg}$ ). After preoxygenation, 3–4 mg/kg of thiopental and 0.1 mg/kg of pancuronium were administered intravenously before tracheal intubation. The lungs were then mechanically ventilated with 60%  $\text{N}_2\text{O}$  in  $\text{O}_2$  using tidal volumes of 10 ml/kg at a rate of 10–12 breaths/min to maintain normocarbida ( $\text{PCO}_2$ , 38–40 torr).

For maintenance of anesthesia, either morphine at rates ranging from 150–250  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ , or fentanyl at rates of 1.5–2.5  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$  was continuously infused. The adequacy of analgesia was based on clinical judgment and depression of somatosensory cortical evoked potentials (approximately 50% of the awake level). The infusion rates of the narcotics were adjusted as indicated by a stress response to surgical stimulus, e.g., hypertension, tachycardia, and sweating. Systolic blood pressure was maintained within 20% of baseline; if hypertension persisted, sodium nitroprusside was infused (1–2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) to return the blood pressure to this level. The narcotic infusions were terminated at the end of the operation just prior to application of the surgical dressings.

Pancuronium (0.02 mg/kg) was added for muscle relaxation as indicated by the nerve stimulator. Patients were kept normothermic (36–37°C), and blood loss was measured and replaced volume for volume. Urine output was measured and maintained at 0.5–1  $\text{ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ . To ensure hemostasis, surgeons injected epinephrine, 1:500,000 in normal saline, into the subcutaneous tissues of the back prior to the incision and into the iliac crest before taking the bone graft.

At the end of the surgical procedure, muscle relaxants were reversed with 0.02 mg/kg of atropine and

Table 1. Demography<sup>a</sup>

Parameter	Morphine	Fentanyl
Male/female	2/8	4/6
Age (yr)	16.4 (12–48)	13.4 (11–25)
Weight (kg)	48.5 (33–73)	48.5 (23.4–77)
Narcotic dose (mg/kg) <sup>b</sup>	0.89 (0.32–1.37)	0.012 (0.005–0.019)
Epinephrine dose ( $\mu\text{g/kg}$ )	5.67 (1.60–9.47)	5.89 (2.67–11.43)
Urine creatinine (mg/ml)		
Preoperative	0.62 (0.35–1.14)	0.56 (0.23–1.37)
Postoperative	0.62 (0.20–1.10)	0.54 (0.24–1.01)

<sup>a</sup>Figures are the means for each group with the range of values in parentheses.

<sup>b</sup>Total amount infused during the operation that lasted from 3.33 to 6.5 hr.

0.04 mg/kg of prostigmine. The patients were extubated when arterial blood gas tensions were acceptable and when negative inspiratory force was  $\geq 20$  cm, tidal volume  $\geq 7$  ml/kg, and respiratory rate  $\geq 10$  breaths/min. Patients were discharged from the recovery room when they were normocapnic ( $\text{PCO}_2$ ,  $40 \pm 5$  torr), normotensive (blood pressure within 20% of the preoperative value), well oxygenated ( $\text{PaO}_2 \geq 80$  torr while breathing room air), and conscious of their surroundings. They were interviewed regarding intraoperative recall while in the recovery room, during the postoperative stay in the hospital, and at the time of their postoperative visit to the surgeon's office.

### Specimen Collection

Arterial blood samples were collected in heparinized syringes and stored on ice for measurements of catecholamines and narcotics at five times: 15 min after induction (narcotic, thiopental, pancuronium, and intubation); 60 min after induction (45 min after the initial infiltration of epinephrine for hemostasis); during laminar decortication; during insertion of the Harrington rod; and during closure.

Arterial blood gas tensions were also measured at these times. Urine samples for catecholamines (glass bottle, 2-ml 5N HCl) were collected via a Foley catheter at two points: after induction but before the incision, and after closure but before leaving the operating room.

### Analytical Procedures

Catecholamines and metabolites were measured by fluorometry (22). Several of the aluminum oxide-extracted plasma samples that were collected during time periods 3, 4, and 5 were also analyzed by high-pressure liquid chromatography with electrochemical

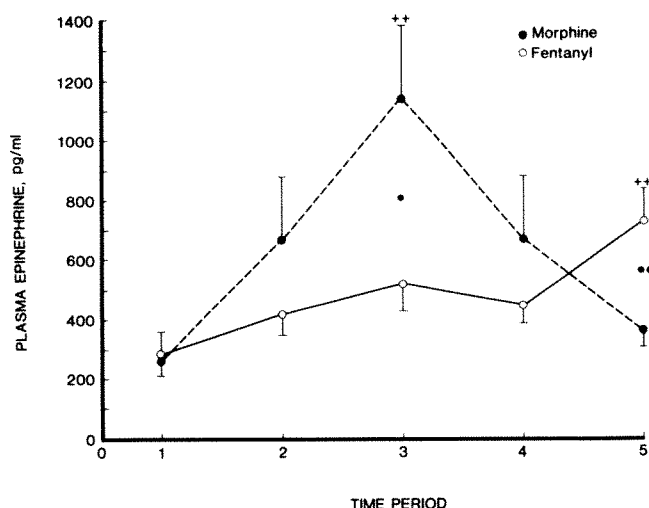


Figure 1. Comparison of plasma epinephrine levels at five time periods during anesthesia with morphine and fentanyl. Each point is the mean  $\pm$  SEM of the results from 10 patients. Symbols at the standard error lines indicate the significance of the difference between each time period and period 1; symbols between the lines represent the significance of differences between the effects of the two narcotics at the same time period. \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ .

detection (LCEC) (23). There was good agreement (within 20%) between them. Values by both techniques were similar, but only the results by fluorometry were used in the calculations. Fentanyl levels were measured by gas chromatography (24) and morphine by LCEC (25).

Data were analyzed by analysis of variance (single and two-way) for repeat measurements with the Newman-Keuls test for significance; by linear regression analysis using the method of least squares, and by paired and unpaired *t*-tests. *P* values of 0.05 or less were accepted as statistically significant.

## Results

The data in Table 1 indicate that the average dose of epinephrine administered was similar in the two groups. Except for the 48-yr old patient in the group receiving morphine and the 25-yr old patient in the group receiving fentanyl, the other patients were close in age, ranging 11–16 yr. Renal function was similar in both groups as shown by the creatinine values; our urinary catechol results are expressed relative to the urinary creatinine concentration. Although we based the initial narcotic doses on a morphine to fentanyl analgesic ratio of 100:1, this ratio is not reflected in the total amounts used because of the differences in the duration of the operations and the relative requirements during the operation.

Plasma levels of epinephrine are summarized in

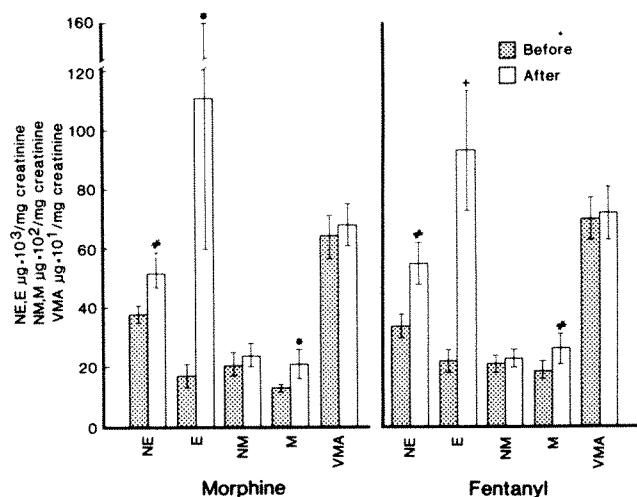


Figure 2. Comparison of urinary catecholamine levels during anesthesia with morphine or fentanyl. Each column is the mean  $\pm$  SEM of the results from 8–10 patients. Before induction ▨; after closure of incision in the operating room □. \*,  $P < 0.05$ ; #,  $P < 0.02$ ; †,  $P < 0.01$ . NE, norepinephrine; E, epinephrine; NM, normetanephrine; M, metanephrine; VMA, vanillylmandelic acid.

Figure 1. Both curves are significantly different from a straight line ( $P < 0.01$ ) and from each other ( $P < 0.01$ ). In period 3, plasma levels of epinephrine were significantly higher in the morphine-treated patients than those receiving fentanyl, but this relationship was reversed in period 5. Comparison of time periods 2–5 with period 1 for each group revealed that in the case of morphine only, the plasma epinephrine level in period 3 was significantly different from period 1, whereas in the group receiving fentanyl, plasma epinephrine at period 5 was significantly elevated over period 1. However, if the data from both groups at period 1 are combined (plasma epinephrine levels at this time were essentially identical in the two groups), then periods 2, 3, and 4 in the group receiving morphine and periods 3, 4, and 5 in the group receiving fentanyl are significantly different from period 1 ( $P < 0.05$ ). Plasma levels of norepinephrine did not change significantly in either group during the five time periods.

The urinary excretion of epinephrine, norepinephrine, and their metabolites before and after the operation is shown in Figure 2. The patterns were similar in the two groups of patients with no significant differences between the relative effects of morphine and fentanyl on the urinary levels of any of the substances measured. However, taking urinary epinephrine plus metanephrine as a measure of the disposition of circulating epinephrine, and considering only the administered epinephrine as the reference figure, we calculated that 6.5% of epinephrine was excreted dur-



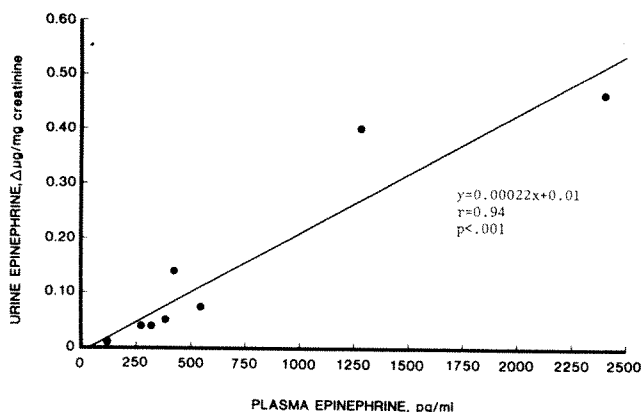


Figure 3. Correlation between epinephrine levels in plasma and urine during anesthesia with morphine. Urinary values are expressed as the difference ( $\Delta$ ) between the post- and preoperative samples.

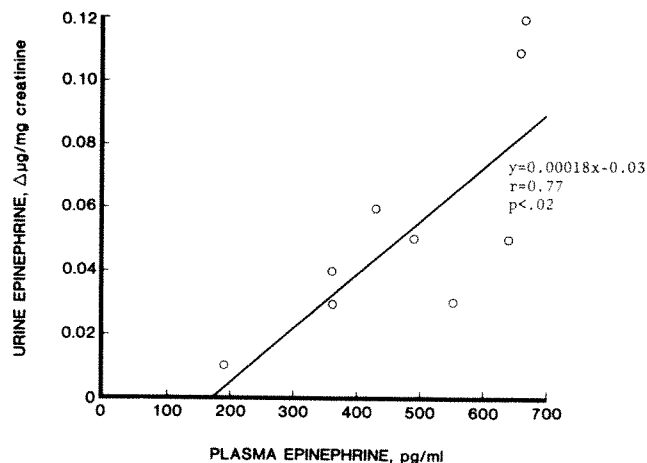


Figure 4. Correlation between epinephrine levels in plasma and urine during anesthesia with fentanyl. Urinary values are expressed as the difference ( $\Delta$ ) between the post- and preoperative samples.

ing the operation by the morphine group, whereas it was 2.4% for the fentanyl group ( $P < 0.05$ ). Not shown are the levels of dopa, dopamine, and homovanillic acid that were essentially unchanged and the same in both groups.

That the urinary excretion of epinephrine was linearly related to its plasma levels is shown in Figures 3 (morphine) and 4 (fentanyl). The linear correlation coefficient for the former was 0.94 ( $P < 0.001$ ) and 0.77 ( $P < 0.02$ ) for the latter.

The plasma levels of the two narcotics are summarized in Figure 5. There was no apparent relationship between these levels and changes in plasma or urinary catecholamine concentrations. The curve for morphine, but not the one for fentanyl, is significantly different from a straight line ( $P < 0.05$ ), and only the concentration of morphine at period 4 is significantly ( $P < 0.05$ ) elevated over the measurement at period 1.

Because sodium nitroprusside was administered as necessary to maintain blood pressure within 20% of the initial value, we could not evaluate the relationship between catecholamines and cardiovascular responses. Nine patients in the morphine group and seven of the fentanyl patients required nitroprusside. The overall plasma epinephrine concentrations in the four patients who did not require nitroprusside were below the mean level for the catecholamine in their respective group.

## Discussion

Several interesting observations were made in this relatively young, healthy, and drug-free population receiving exogenous epinephrine. Clinically, the two groups of patients appeared to be equally well an-

esthetized, and yet fentanyl was more effective than morphine in modulating the catecholamine stress response to the operation. Plasma epinephrine levels increased less than twofold in the group receiving fentanyl but more than fourfold in the group receiving morphine at time period 3, when the most stressful aspect of the operation was in progress. This difference cannot be attributed to altered absorption of epinephrine because it would have been complete by this time; also, if a different degree of local vasoconstriction had occurred to modify absorption, the plasma levels of epinephrine would have decreased rather than increased. A release of catecholamines by morphine also cannot be invoked because an equivalent increase was not obtained at period 1 after the bolus injection of the narcotics. We did not measure plasma catecholamine concentrations prior to induction; however, the levels in period 1 are in the range previously obtained in surgical patients under similar conditions (unpublished data).

A possible histamine-mediated effect also can be excluded because there was no clinical indication, e.g., transient hypotension or flushing, of the involvement of this autocoid. Our patients intraoperatively experienced hypertension rather than hypotension, and again, except for the initial bolus dose, plasma levels of morphine during the operation would have been too low to release a significant amount of histamine (17).

Conceivably, in the present study insufficient morphine was administered; however, clinically and on the basis of depression of somatosensory cortical evoked potentials, the two groups of patients appeared to be equally well anesthetized. Rather, we

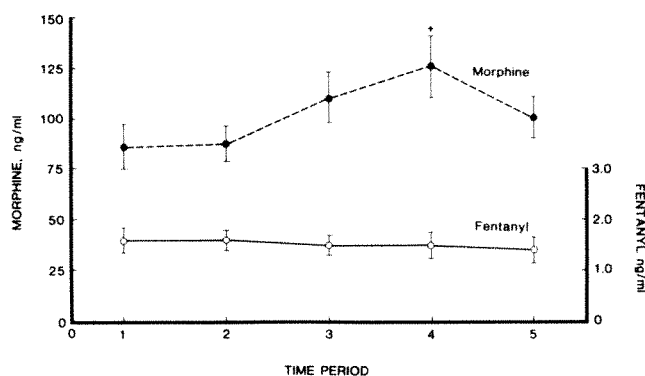


Figure 5. Plasma levels of morphine and fentanyl at five time periods during spinal surgery. Each point is the mean  $\pm$  SEM of the results from 10 patients. Time periods 2-5 are compared to period 1 within each curve. †,  $P < 0.05$ .

postulate that the underlying mechanism for the increase in plasma epinephrine at period 3 in the group receiving morphine was a pain-induced, neurogenic-mediated release of epinephrine from adrenergic nerve endings and the adrenal medulla, an effect independent of morphine levels. We offer two reasons for this interpretation: first, the peak plasma levels of morphine and epinephrine are out of phase (Figs. 1 and 5) and, second, exogenous epinephrine can function as a false transmitter at adrenergic nerve endings with a much lower affinity than norepinephrine for storage sites (26,27). Thus after uptake into adrenergic nerve endings, the exogenous epinephrine would be more readily released than norepinephrine upon sympathetic stimulation, the response being more vigorous in the less obtunded morphine-treated patients. This may explain why the plasma levels of norepinephrine did not change intraoperatively to any great extent when they would have been expected to do so. For example, in a recent study in the same type of patients receiving morphine as part of the anesthetic protocol, the epinephrine response was almost as vigorous as that for norepinephrine (28). That plasma norepinephrine did increase in our patients during the operation is reflected by the increase in urinary levels in the "after" sample, but the increase was much less than that obtained with epinephrine (Fig. 2). In addition to the stress of the operation, part of the increase may also be attributed to displacement by a mass effect of the exogenous epinephrine, which would be stored in the same elements of the adrenergic nerve endings as norepinephrine. It should be pointed out that we do not know how much of the plasma epinephrine was derived from endogenous and exogenous sources; nor do we know to what extent the adrenal medulla and adrenergic nerve endings each contributed to these amounts except that the adrenal

medulla would be the source for the endogenous epinephrine.

An important advantage of small-dose fentanyl over morphine as an anesthetic is its apparent shorter duration of action. The group receiving fentanyl was much more responsive to stimuli in period 5 than the morphine-treated patients. The operation was over and the narcotics had been discontinued at this time. This was accompanied by a marked increase in plasma epinephrine in the group receiving fentanyl, an effect absent in the still obtunded morphine-treated patients. And it occurred in spite of the fact that the plasma level of fentanyl in period 5 was not significantly lower than the earlier ones. However, we do not know the brain levels of fentanyl at this time. The equilibrium for fentanyl would be expected to shift from brain to plasma more rapidly than for morphine, because fentanyl is more lipid soluble than morphine. A recent report by Ghonheim et al. (29) supports this contention; they found mental function to return more rapidly in fentanyl-treated patients compared with those treated with morphine. Three of our morphine-treated patients, but none in the fentanyl group, required ventilatory support in the recovery room. Questioning the patients in the recovery room and later during a followup visit revealed that all were amnesic for the perioperative period and none recalled any discomfort during the operation.

The similar pattern in the urinary excretion of the catecholamines and their metabolites suggests that under these conditions both narcotics exert a qualitatively similar effect on the metabolism and disposition of epinephrine and norepinephrine.

Finally, from the data on the plasma levels of the narcotics, it appears that a constant and effective narcotic level can be readily attained by infusions, particularly with fentanyl. This agrees with our previous study in a similar group of patients in which we demonstrated the advantage of fentanyl over morphine, particularly when administered as a continuous infusion rather than as a bolus injection (16).

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## Vecuronium and Porcine Malignant Hyperthermia

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BUZELLO W, WILLIAMS CH, CHANDRA P,  
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*Vecuronium was studied in eight malignant hyperthermia (MH) susceptible pigs for its potential to either trigger or prevent MH. Two sets of experiments were performed in the same animals: 1-hr total neuromuscular blockade by vecuronium infusion with thiopental anesthesia in the absence of invasive monitoring and halothane; and 1-hr infusion of vecuronium with thiopental anesthesia with invasive monitoring in the absence of and then, followed by 30-min infusion in the presence of halothane, followed in turn by exposure to halothane alone. One-hour infusion of vecuronium in the absence of halothane and invasive monitoring did not trigger MH in any animal. During the*

*second set of experiments, MH, evidenced by rising rectal temperature, elevated end-tidal PCO<sub>2</sub>, mixed venous oxygen desaturation, and muscle rigor, occurred in one animal during vecuronium alone, in four animals during vecuronium infusion and simultaneous exposure to halothane, and in three animals during exposure to halothane alone after recovery from vecuronium neuromuscular blockade. In view of the results of control experiments, the development of MH during vecuronium neuromuscular blockade before exposure to halothane was attributed to surgical stress rather than to vecuronium itself. It is concluded that vecuronium is not a trigger to MH in susceptible pigs.*

Key Words: NEUROMUSCULAR RELAXANTS—  
vecuronium. HYPERTHERMIA—malignant.

The new nondepolarizing muscle relaxant, vecuronium, has been reported to be almost devoid of side effects (1,2). As a nondepolarizing muscle relaxant it should not trigger MH. Yet, this can not be taken for granted, because in a clinical report Britt et al. (3) incriminated curare as a possible triggering agent. Other studies have shown that depolarizing muscle relaxants will trigger MH (4). Therefore, the present study has been designed to investigate the MH triggering potential of vecuronium.

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### Materials and Methods

The study was conducted in eight outbred MH-susceptible Poland China pigs of a colony whose lines have been maintained for the past 14 years. At 8-10 weeks old, a halothane screening test for MH susceptibility was performed (5). At 15-20 weeks old and 50-70 kg body weight, each animal underwent two consecutive sets of experiments.

#### *Prolonged Vecuronium Neuromuscular Blockade in the Absence of Both Halothane and Invasive Procedures*

The unpremedicated pigs were anesthetized by intraperitoneal injection of thiopental, 25 mg·kg<sup>-1</sup>. An ear vein was cannulated, and 1-4 mg·kg<sup>-1</sup> increments of thiopental were injected intravenously as needed. Orotracheal intubation was performed without the aid of a muscle relaxant. Mechanical ventilation with room air then was instituted by means of a Harvard pump in a nonrebreathing circuit, ventilation was adjusted to maintain end-tidal PCO<sub>2</sub> of 35-40 torr, as monitored continuously by infrared absorption capnography. Additional monitoring included ECG lead II, heart rate, and rectal temperature. Neuromuscular transmission was assessed by recording evoked twitch

tension in response to supramaximal train-of-four stimulation (0.2-msec square pulses, 2 Hz, 15 sec apart) of the left peroneal nerve via needle electrodes. A Grass FT 10 force displacement transducer was attached to the left rear foot. When a stable base line recording had been obtained, a loading dose of  $0.4 \text{ mg} \cdot \text{kg}^{-1}$  vecuronium (two times the average cumulative 90% blocking dose (5)) was injected intravenously and an autosyringe delivering a constant intravenous infusion of 16 times the cumulative 90% blocking dose per hour was started at the same time. The infusion was discontinued after 60 min, and the pigs were allowed to recover.

Elevated rectal temperature over  $41^\circ\text{C}$  after a temperature increase of more than  $0.05^\circ\text{C}/\text{min}$ , end-tidal  $\text{PCO}_2$  over 80 torr, tachyarrhythmia, and extension rigor of the legs were used as diagnostic criteria of MH. The ventilation rate was not changed from the control settings; therefore, the  $\text{PCO}_2$  rapidly increased whenever MH developed.

#### *Prolonged Vecuronium Neuromuscular Blockade and Invasive Monitoring in the Absence and in the Presence of Halothane*

One week after the first experiment, the same animals were studied again. The protocol is illustrated by Figure 1. Anesthesia was induced as described before and maintained by mechanical ventilation with 70% nitrous oxide in oxygen in a semiclosed circuit with 5 L/min fresh gas flow. The efficiency of  $\text{CO}_2$  absorption was continuously monitored by capnography. Increments of thiopental ( $1\text{--}4 \text{ mg} \cdot \text{kg}^{-1}$ ) were injected intravenously as needed. ECG, heart rate, arterial, pulmonary artery and central venous pressure, arterial and mixed oxygen saturation (Opticath-Oximatrix system), rectal and blood temperatures,  $\text{PCO}_2$  of the inhaled and exhaled gas, and evoked twitch tension were recorded continuously by a polygraph. After completion of the surgical procedure, nitrous oxide was discontinued, and the pigs were ventilated with oxygen. Arterial and mixed venous blood gas analysis was performed at the end of nitrous oxide anesthesia, after the first 20 min of 100% oxygen, after 60 min of vecuronium infusion, and during MH at 20-min intervals. The results were corrected for actual blood temperature. The results of arterial and mixed venous oxygen saturation were used as calibration standards for the Oximatrix system. After 20 min of stable baseline recording, vecuronium was administered as described above. The vecuronium infusion was maintained for 60 min in the absence of and for 30 min in the presence of halothane 2 vol % inspiratory concentration.

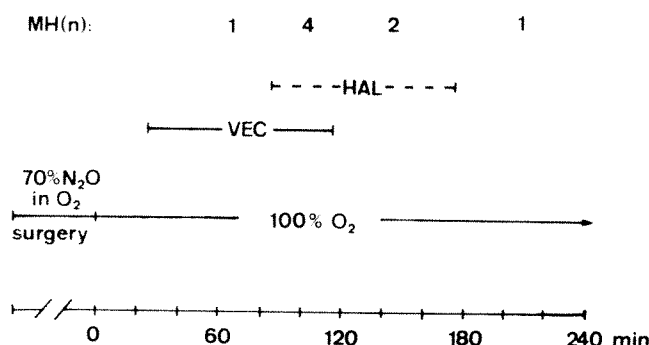


Figure 1. Protocol of experiment number 2. Digits on top (MH(n):) give numbers of pigs exhibiting MH at different steps of the experiment. Vecuronium was given by infusion at the rate of ( $0.4 \text{ mg} \cdot \text{kg}^{-1}/3.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ). Halothane was given at 2 vol %.

In case of severe arterial hypotension, halothane was reduced to 1.0–0.5 vol % or its administration was discontinued. Halothane administration was also discontinued if the onset of MH was associated with arterial hypotension secondary to severe cardiac dysrhythmia. If halothane failed to trigger MH in the presence of vecuronium, its administration was continued until, after the end of vecuronium infusion, neuromuscular transmission was completely restored or MH developed. All results are given as means and standard deviation ( $\bar{x} \pm \text{SD}$ ). Paired *t*-tests were used to assess statistical significance.

## Results

### *Prolonged Vecuronium Neuromuscular Blockade in the Absence of Halothane and Invasive Procedures*

The  $0.4 \text{ mg} \cdot \text{kg}^{-1}$  loading dose followed by the  $3.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$  infusion of vecuronium created total neuromuscular blockade in all eight animals. The total dose used was  $192 \pm 53 \text{ mg}$  per animal. After cessation of the infusion, it took  $6 \pm 3 \text{ min}$  to recover 25% and another  $12 \pm 5 \text{ min}$  to recover 75% of control twitch tension (recovery time). No significant changes in heart rate, rectal temperature or end-tidal  $\text{PCO}_2$  occurred during the 1-hr infusion of vecuronium (Fig. 2), nor did cardiac dysrhythmia or muscle rigor occur in any animal. All pigs recovered readily from anesthesia and were utilized in the second set of experiments.

### *Prolonged Vecuronium Neuromuscular Blockade and Invasive Monitoring in the Absence and in the Presence of Halothane*

The results of this experiment are also illustrated by Figure 2. When vecuronium was started, the initial

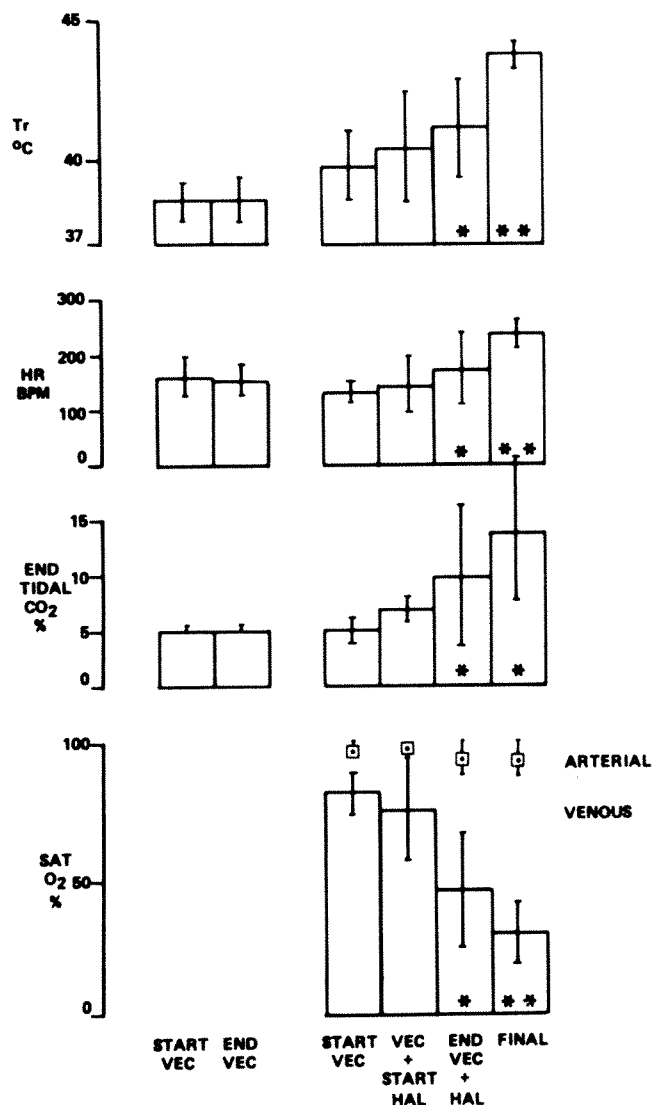


Figure 2. Modification of rectal temperature (Tr), heart rate (HR), end tidal  $\text{PCO}_2$ , and mixed venous and arterial  $\text{O}_2$  saturation ( $\text{SATO}_2$ ) in response to continuous infusion of vecuronium in the absence of and in the presence of halothane ( $\bar{x} \pm \text{SD}$ ). No significant difference in Tr, HR,  $\text{ETCO}_2$  or  $\text{SATO}_2$  occurred during the 1-hr infusion of vecuronium. A significant difference (\*)  $P < 0.05$  was observed in Tr, HR,  $\text{ETCO}_2$  and  $\text{VO}_2$  saturation. A more highly significant difference (\*\*)  $P < 0.01$  was observed in Tr, HR, and  $\text{VO}_2$  saturation during exposure to halothane.

temperatures were significantly higher than in the previous experiment ( $39.8 \pm 1.3$  vs  $38.6 \pm 0.7^\circ\text{C}$ ). After induction of anesthesia, animal number 1 had a rectal temperature of  $39.4^\circ\text{C}$ , which was the same as in the beginning of the first experiment. During the next 3 hr required for surgery and baseline recording, the temperature in this animal increased to  $41.3^\circ\text{C}$  ( $0.016^\circ\text{C}/\text{min}$ ). At this point the administration of vecuronium was started, and, after another 22 min of complete neuromuscular blockade, rectal temper-

ature increased sharply to  $44.9^\circ\text{C}$  ( $0.09\text{--}0.1^\circ\text{C}/\text{min}$ ). Concomitantly, venous  $\text{O}_2$  saturation decreased from 96 to 23%, end-tidal  $\text{PCO}_2$  increased to 102 torr from 49 torr, and tachyarrhythmia (263 beats/min) and severe extension rigor of the legs were observed. The animal died 18 min after the end of one hour's infusion of vecuronium without having been exposed to halothane (Fig. 3(A)).

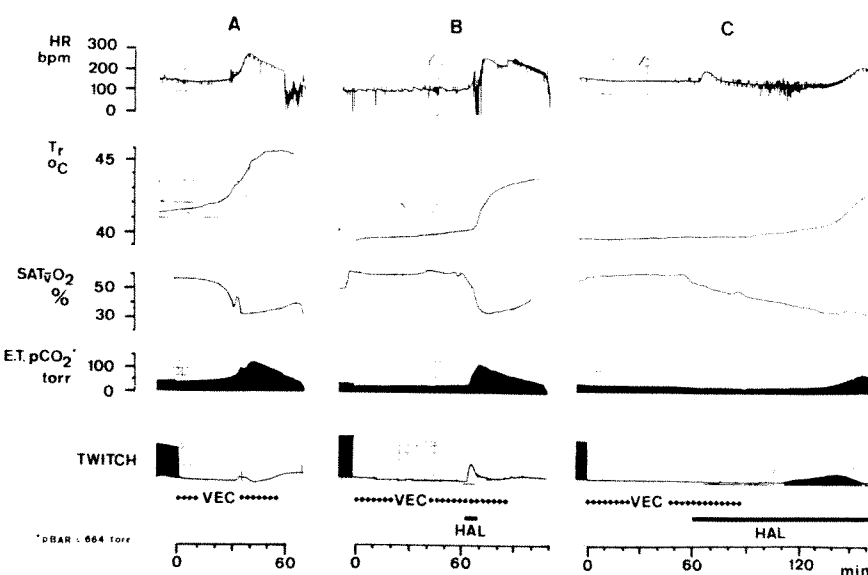
The remaining seven animals, six of which also had an initial temperature higher than  $39^\circ\text{C}$ , did not show any further signs heralding the onset of MH during vecuronium infusion and in the absence of halothane. Before and after the 60 min infusion of vecuronium, the following were recorded in these 7 animals: rectal temperature  $39.6 \pm 1.2$  and  $39.8 \pm 1.0^\circ\text{C}$ , heart rate  $102 \pm 25$  and  $128 \pm 24$  beats/min, end-tidal  $\text{PCO}_2$   $33 \pm 5$  and  $33 \pm 6$  torr, arterial  $\text{O}_2$  saturation  $99.4 \pm 1.4$  and  $99.2 \pm 0.8\%$ , mixed venous  $\text{O}_2$  saturation  $83 \pm 7$  and  $83 \pm 3\%$ . None of these changes were statistically significant. Cardiac dysrhythmia or muscle rigor did not occur. During an additional 30 min of infusion of vecuronium in the presence of halothane, rectal temperature, heart rate and end-tidal  $\text{PCO}_2$  increased sharply, while mean mixed venous  $\text{O}_2$  saturation decreased to  $46 \pm 20$  (16–52%). At this point, no significant change was seen in arterial  $\text{O}_2$  saturation. Rectal temperature increased as rapidly as  $0.1^\circ\text{C}/\text{min}$  and all animals developed severe extension rigor of their legs. No animal survived this condition.

Figure 1 indicates the incidence of MH at particular stages of the experiment. Secondary to their exposure to halothane, 4 pigs (numbers 2, 3, 5, and 8) died in the presence of vecuronium neuromuscular blockade. In two of them (numbers 5 and 8) 4 min of halothane inhalation was sufficient to trigger the full blown MH syndrome (Fig. 3 (B)). Another three pigs developed lethal MH only during (numbers 4 and 7) or after (number 6) their exposure to halothane alone. However, in animals number 4 (Fig. 3 (C)) and 7 a continuously declining mixed venous  $\text{O}_2$  saturation was already recorded from the beginning of halothane inhalation, and it was only when neuromuscular transmission started to recover that hyperthermia, tachyarrhythmia, hypercarbia and muscle rigor were initiated. Animal number 7 died from MH in the absence of muscle rigor.

## Discussion

*d*-Tubocurarine, pancuronium, metocurine, and recently, atracurium have been shown not to trigger MH in susceptible pigs (6–12). Correspondingly, in the present study, MH was not observed during vecuronium nondepolarizing neuromuscular blockade





**Figure 3.** Recordings of three animals with MH at different stages of the experiment. (*Panel A*) MH occurring during vecuronium infusion in the absence of halothane (animal No. 1). (*Panel B*) MH triggered by only four min exposure to halothane in the presence of vecuronium neuromuscular blockade. Muscle rigor reflected by transient elevation of the baseline of twitch recording (animal No. 9). (*Panel C*) Mixed venous O<sub>2</sub> desaturation heralding halothane induced MH which became manifest only upon partial recovery of neuromuscular transmission (animal No. 4).

in the absence of halothane and surgery (experiment no. 1). The results were duplicated in the same animals by experiment no. 2, with the exception of one animal, where MH occurred during vecuronium neuromuscular blockade before halothane could be administered. The relationship between vecuronium and MH thus appears debatable.

In the seven halothane-related cases of MH in experiment no. 2, both the fulminance of the syndrome and its relation to different steps of the experiment were variable. Uniformly, however, in these seven animals, rectal temperature, heart rate, end-tidal PCO<sub>2</sub> and mixed venous O<sub>2</sub> saturation were remarkably stable in the presence of vecuronium neuromuscular blockade as long as halothane administration was withheld. In particular, mixed venous O<sub>2</sub> saturation, which has been reported to be the most sensitive parameter to herald incipient MH (19), decreased only upon administration of halothane. Thus the initiation of MH in these seven animals was clearly to be attributed to halothane, whereas vecuronium did not affect any parameter indicative of MH. Similar observations have been published by other investigators. *d*-Tubocurarine was found to prevent succinylcholine- (6), but not halothane-induced MH, whereas pancuronium (0.2 mg·kg<sup>-1</sup>) provided some protection against the triggering effect of halothane (9,10). Metocurine (2 mg·kg<sup>-1</sup>) prevented halothane-induced MH in 13 out of 14 pigs (10–12). The dose of metocurine was more than 65 times the one required for just total twitch depression. In contrast, the block produced by *d*-tubocurarine and pancuronium (10)

was comparable to a clinical level of muscle relaxation, because the authors were able to restore the twitch response with 5.0 mg of neostigmine. In the present study after the end of the vecuronium infusion, the recovery of neuromuscular transmission was much faster than after smaller doses in humans (13). Therefore, in this study, the level of vecuronium neuromuscular blockade might also have represented a clinical type of muscle relaxation rather than a true 100% receptor occlusion. It may thus be theorized that in several animals a certain quantity of unblocked cholinergic receptors may have allowed for some membrane depolarization sufficient to initiate MH. It is also open to question whether mixed venous oxygen desaturation is in fact related to depolarization of the muscle membrane (14) or whether this part of the metabolic derangement is initiated by a mechanism unrelated to membrane depolarization, i.e., futile cycling (15). Should high doses of nondepolarizing muscle relaxants be effective in preventing excessive oxygen extraction, they may act by a mechanism unrelated to neuromuscular blockade. The present study was not designed to test or to elucidate these mechanisms.

The concept that vecuronium, like other nondepolarizing muscle relaxants, does not trigger MH, is challenged by the development of MH in one pig during vecuronium infusion in the absence of halothane. In view of these considerations, it appears also open to question, whether in one animal in the absence of halothane, MH occurred during, due to or in spite of vecuronium neuromuscular blockade. This pig was highly susceptible to MH as evidenced by

stiff extension rigor of his legs after only 3 min of halothane inhalation during the screening test at 8 weeks of age and by the 39.4°C rectal temperature at the beginning of experiment no. 1. At eight weeks of age, as part of a pilot study, the same pig underwent uneventful vecuronium dose-response testing under thiopental anesthesia (5). In experiment no. 1 of the present study, both the rectal temperature and the heart rate of this pig were somewhat lower after the 60 min vecuronium infusion than before (39.2 vs 39.4°C and 139 vs 154 beats/min). In the second experiment, rectal temperature was 39.4°C at the beginning of surgery and 41.3°C when vecuronium neuromuscular blockade was initiated. Yet, 22 min of vecuronium infusion were tolerated without any signs of beginning MH. In particular, no mixed venous oxygen desaturation was recorded, and the increase in rectal temperature was only 0.027°C/min. In view of this animal's positive response to halothane in the screening test, uneventful tolerance of vecuronium administration on two previous occasions and of the considerably delayed manifestation of MH during the last vecuronium infusion, we conclude that in this animal the initiation of MH in the absence of halothane was unrelated to or may even have been delayed by co-existing vecuronium neuromuscular blockade. Surgical stress and 1-hr indirect muscle stimulation before the initiation of neuromuscular blockade are more likely to have triggered the syndrome, because rectal temperature had already increased during this period. The same sequence of events was recorded during an invasive experiment in one more pig that was part of a four-animal pilot study and that prompted us to incorporate the noninvasive control experiment into the final protocol of the present study. In view of previously published data on the spontaneous development of MH in our strain of susceptible pigs (16) we conclude that vecuronium does not trigger MH in susceptible pigs.

In an attempt to imitate the human clinical condition as closely as possible, a population of outbred MH-susceptible pigs was preferred to the use of inbred animals. Accordingly, both the fulminance of the syndrome and the pattern of its course were extremely variable. The data demonstrate that when testing drugs for their MH-triggering potential, the full blown syndrome may become manifest anytime between a few minutes to more than one hour's exposure of the animal to the triggering agent in question, or even secondary to nonspecific stress. The initiation of MH may be missed unless mixed venous O<sub>2</sub> saturation is continuously recorded, and the condition may be lethal even in the absence of muscle rigor (17).

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## Review Article

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# Anesthesia and Intraocular Pressure

Dermot F. Murphy, FFARCSI

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Major advances in the highly specialized field of intraocular surgery have been made in recent years. The greatly increased use of general anesthesia in ophthalmic surgery bears witness to the significant contribution made by the anesthesiologist in this regard.

Because of the development of improved anesthetic agents and techniques, the anesthesiologist can optimize conditions for such surgery. Apart from providing an immobile and uncongested field he can, by manipulating the factors at his disposal, decrease intraocular pressure and thus minimize the danger of expulsion of intraocular contents when the eye is opened. The aim of this paper is to review the physiological and pharmacological factors involved in attaining this goal by summarizing the factors normally involved in control of intraocular pressure and thereafter outlining how manipulation of these factors during anesthesia can improve conditions for intraocular surgery.

### Physiological Determinants of Intraocular Pressure

Intraocular pressure (IOP) is defined as the pressure exerted by the contents of the eye against its containing wall. This pressure is determined by the volumes of the various components within the eye, which cause pressure to be exerted outwards, and the intrinsic compliance and external compressive forces, which cause pressure to be exerted inwards. The components within the eye that can undergo significant changes in volume include aqueous humor and blood, and it is changes in these volumes that can significantly alter intraocular pressure. Other intraocular

components can undergo changes in volume, but these are unimportant in the present context. The degree of compliance of the scleral and corneal walls can vary from eye to eye, but for an individual eye, is not subject to significant change.

External compression of the globe, either through extraocular muscle contraction or otherwise, can increase IOP directly but can also have indirect effects by inducing changes in the volumes of the intraocular components.

Intraocular pressure is considered normal within the range of 10–20 mm Hg, but may range more widely in the general population (1). A diurnal variation of 2–3 mm Hg is normal.

It should be emphasized that this review will deal only with factors that can cause acute changes in IOP. Factors involved in chronic alteration of IOP are of little relevance to the anesthesiologist.

### Factors Affecting Intraocular Blood Volumes

Together with factors affecting intracranial blood volume, intraocular blood volume depends on a balance between the rate of blood inflow to and the rate of blood outflow from the eye. Apart from this, the baseline intraocular blood volume depends on the degree of constriction of the intraocular blood vessels.

#### *Effect of Change of Systemic Arterial Pressure on IOP*

As with many other organs, the eye is capable of autoregulation of its blood supply and thus only a poor correlation exists between changes in systemic arterial pressure and intraocular pressure. Such a correlation was studied in young adult cats by Macri (2). After pentobarbital anesthesia, the femoral, ophthalmic, and long posterior ciliary arteries, and the anterior chamber of the eye were cannulated. Thereafter, changes of pressure in each component were

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plotted against changes in systemic arterial (femoral) pressure. A highly significant direct correlation was found between the femoral and ophthalmic artery pressures, but no correlation existed between the pressures of the ophthalmic and iris (long posterior ciliary) arteries. A significant direct correlation was, however, found between the iris artery pressure and intraocular pressure. Macri concluded that a dissociation occurred between the iris artery and the ophthalmic artery such that changes in systemic arterial pressure were poorly transmitted to the eye. Schreuder and Linssen (3) reported similar results: decreases in aortic pressure to 60% below control values were not accompanied by changes in intraocular pressure. Administration of vasopressors increased intraocular pressure but to levels that did not correlate with the concomitant rise in arterial pressure.

Friedman (4) addressed the question of regulation of choroidal blood flow. Using a range of systemic arterial pressure of 25–215 mm Hg and intraocular pressures of 0–120 mm Hg, he made more than 1000 measurements of choroidal blood flow in cats under pentobarbital anesthesia and measured the relationship between intraocular pressure and choroidal blood flow. He found that, in general, choroidal blood flow was directly related to perfusion pressure, with intraocular pressures up to 30 mm Hg. Some evidence of active choroidal blood flow autoregulation was found above this intraocular pressure. He did not attempt to correlate intraocular pressure changes with changes in systemic or choroidal arterial pressures. In a clinical study on the effects of hypotensive anesthesia, Tsamparlakis et al. (5) correlated changes in intraocular pressure with systemic arterial pressure and found that two groups of patients could be identified; in those with an initially low IOP, a significant correlation was found between IOP and both systemic arterial and venous pressures. In patients with an initial IOP greater than 11 mm Hg, they found no correlation with arterial pressure but a good correlation between IOP and central venous pressure.

It appears from these and other studies (6–8) that arterial pressure plays some role in intraocular pressure control but that, over a physiological range of arterial pressure, this effect is relatively minor.

#### *Effect of Change in Venous Pressure on IOP*

With an elevation in central venous pressure, blood efflux from the eye is inhibited, resulting in an increase in IOP. The importance of venous pressure in altering IOP is well established. In 1926, Duke-Elder (9) found a significant correlation between venous pressure and IOP in dogs. Macri (10,11) found a sim-

ilar correlation in cats that was so exact that a simple mathematical expression described the relationship.

By cannulating the anterior chamber and one of the anterior ciliary or vortex veins, Macri (11) was able to independently alter anterior chamber and venous pressures and study their interdependence. In both intact and enucleated eyes, increasing venous pressure caused parallel changes of similar magnitude in anterior chamber pressure. Decreasing venous pressure caused a decrease of similar magnitude in IOP. On the basis of these results he suggested that "changes of the venous pressure produce or result from corresponding changes in the diameter of intraocular blood vessels (most probably the vessels of the ciliary processes)." He also suggested that "changes in vessel diameter then change intraocular pressure simply by their effects on the intraocular volume."

Whereas Macri thought it important not to extrapolate his results to suggest a similar relationship in humans, other authors have shown, albeit less precisely, that a close correlation exists between central venous pressure (CVP) and IOP in humans (5,12,13). Of particular relevance in the present context are studies that demonstrate the effect of posture on venous pressure and thus IOP. Hvidberg et al. (12) found instantaneous parallel changes in CVP and IOP with alterations from Trendelenburg to head-up positions. Similar changes in IOP with posture were reported by Williams and Peart (14), Kriegelstein and Langham (15) and Tsamparlakis et al. (5). The importance of a slight head-up tilt for reduction of IOP during intraocular surgery is stressed by these authors.

#### *Effect of Change of Basal Intraocular Blood Volume on IOP*

Factors affecting blood inflow to and blood outflow from the eye have been mentioned. In an equilibrium state, the other factor affecting intraocular blood volume is the tone of the intraocular vessels, because alteration in vascular tone alters the capacitance of these vessels. Intraocular vascular tone is predominantly affected by arterial  $PCO_2$  and by central controlling areas in the diencephalon.

The effect of changes in  $PCO_2$  on IOP is well documented (12,13,16–21). Samuel and Beaugie (17) studied the effect of different end-tidal concentrations of  $CO_2$  on IOP in patients without ophthalmic symptoms. They found that, although CVP remained unchanged, a straight line correlation existed between IOP and end-tidal concentrations of 3, 5, and 8%  $CO_2$ . They postulated that a decrease in IOP could result from vasoconstriction of the choroidal blood vessels, from a decrease in aqueous formation, which is controlled by the enzyme carbonic anhydrase, under the



influence of  $\text{PCO}_2$ , or a combination of both. Hvidberg et al. (12) studied the effect of changes in  $\text{PCO}_2$  and body positions on IOP during general anesthesia and found a similar correlation between  $\text{PCO}_2$  and IOP. These authors hypothesized, however, that changes in IOP occurred so rapidly with changes in  $\text{PCO}_2$  that they could not be explained on the basis of altered aqueous formation. They found, moreover, that changes in  $\text{PCO}_2$  were accompanied by parallel changes in CVP and concluded that an increase in IOP after an increase in  $\text{PCO}_2$  occurred as a result of choroidal vasodilation or elevation in CVP or, more likely, a combination of both mechanisms. More recently their findings were confirmed by Petounis et al. (19). These authors found that the increase in IOP as a result of increased  $\text{PCO}_2$  was not prevented by pretreatment with acetazolamide, an inhibitor of aqueous formation. They concluded that an increase in CVP along with choroidal vasodilatation caused IOP elevation after hypoventilation. Smith et al. (18) maintained a stable CVP at different values of  $\text{PCO}_2$  and still found a linear correlation with IOP. They concluded that intraocular vasodilatation must be the cause. Spalter et al. (21) photographed the retinal vessels at different levels of  $\text{PCO}_2$  and found this to be true. Using a radioactive krypton-desaturation technique, Friedman and Chandra (22) confirmed that choroidal vascular resistance varied directly with the concentration of inhaled  $\text{CO}_2$ .

The central control of IOP is complex because it involves control of vascular and extraocular muscle tone apart from a possible direct effect on intraocular pressure per se. Nevertheless, specific areas of the diencephalon have been isolated that have been shown to have specific actions on intraocular tension.

Von Sallman and Lowenstein (23), in painstaking stereotaxic experiments, attempted to isolate areas in the cat diencephalon responsible for changes in IOP. They also attempted to ascertain whether these changes were necessarily accompanied by changes in other variables such as arterial pressure or motor tone. The most frequently occurring responses fell into three groups depending on the location of the stimulating electrodes. "Gradual responses" in eye pressure occurred that closely mimicked those seen after intravenous administration of adrenostimulatory drugs, in the absence of discernable intraocular muscle reactions. These "responses" coincided with parallel changes in arterial blood pressure. "Fast responses" occurred when the slope of the change in pressure was steep. These responses in IOP usually were accompanied by rapid maximal dilatation of the pupils and evidence of extraocular smooth muscle contraction, leading the authors to consider a cause-and-effect

relationship. "Very fast responses" in IOP changes were accompanied by extraocular striated muscle contraction. In addition to these associations, parallel variations in systemic blood pressure were found with both fast responses indicating that participation of neurovascular events was superimposed on extraocular muscle contraction.

Schmerl and Steinberg (24) found that they could isolate areas of the diencephalon to prove that pupillary motility and control of intraocular tension were mutually exclusive. They did not speculate as to the mechanism of central control of intraocular pressure.

## Factors Affecting Intraocular Aqueous Volume

### *Effect of Change of Aqueous Humor Formation on IOP*

Aqueous humor is formed both by ultrafiltration from plasma through the ciliary epithelium and by active secretion from these cells. Because of the difficulty in measuring its rate of formation, the relative importance of each route is disputed. Proportions between 20 and 80% have been proposed for each route (25,26). Control of aqueous humor formation is poorly understood and central controlling areas have not been isolated.

Both stimulation and depression of aqueous formation have been reported after administration of drugs with sympathetic and parasympathetic effects (27-29), and changes in systemic arterial pressure have been shown to depress aqueous formation only when reduced to levels incompatible with adequate perfusion (30).

There have been some suggestions of depression of aqueous formation by anesthetic drugs (31,32), but their effect on outflow facility is thought to be more important (see below).

Acetazolamide (Diamox) has a significant effect on aqueous formation and thus has been used widely in the treatment of glaucoma (33-36). The most important action of acetazolamide is inhibition of the enzyme carbonic anhydrase, which is present on the nonpigmented cells of the ciliary process, where it plays an important role in the formation of aqueous humor (37,38). Friedland et al. (35) studied the short-term dose-response characteristics of oral acetazolamide in patients with ocular hypertension and found that maximal reduction of IOP (30-35% below control levels) occurred 2 hr after its administration, thus making it ideal for preoperative administration. Even greater reductions in IOP have been reported after its chronic use (33,36,39).

It has been suggested that  $\beta$ -adrenergic blocking drugs decrease intraocular pressure by depressing aqueous formation, but evidence for this mechanism of action is still inconclusive (36,39).

### *Effect of Change of Aqueous Drainage of IOP*

Drainage of aqueous humor occurs by two routes. The main route is entrance of aqueous humor into the anterior chamber via the pupil and thence laterally to the iridocorneal angle. From there most of the aqueous enters Schlemm's canal by passing through three layers of meshwork that separate the anterior chamber from the canal. A smaller proportion of aqueous moves through the interstitial spaces of the ciliary muscle and leaves the eye through the substances of the sclera.

Resistance to outflow of aqueous was studied extensively by Grant (40). In enucleated normal, pathological, and experimentally pathological eyes, he assessed the effect of a variety of manipulations on experimental aqueous perfusion and outflow. Most significant was a 75% reduction in outflow resistance when the trabecular meshwork between the anterior chamber and Schlemm's canal was disrupted, proving this meshwork to be the primary controller of outflow. Contraction of the ciliary muscle has been shown to decrease resistance to outflow and it is proposed that opening the trabecular meshwork is the main effect of this maneuver (41).

Resistance to outflow drainage is also influenced by adrenergic stimulation. Langham et al. (42) studied the effects of topical epinephrine, norepinephrine, and isoproterenol on aqueous humor dynamics, intraocular pressure, and pupillary size. He found that  $\alpha$ -stimulation induced mydriasis, a decrease in IOP, and increased tonographic outflow facility;  $\beta$ -stimulation decreased IOP without affecting pupillary size or outflow facility; epinephrine administrations caused  $\beta$ -stimulatory effects at low doses, and  $\alpha$ -stimulation at higher dosage. It was postulated that alteration of blood flow through the ciliary processes was the main mechanism by which these various responses were effected.

Some anesthetics increase aqueous outflow facility, contributing in part to their effect in decreasing IOP (32). Their effects on IOP are, however, complex and it is likely that this mechanism is only of minor importance.

### *Effect of External Compression on Intraocular Pressure*

Whereas sudden external compression of the eye elevates IOP, compensatory effects are also induced

that offset this increase in pressure. Elevated pressure within the eye might be expected to have an effect on aqueous outflow facility and thus on aqueous and vitreous volumes as well as on intraocular blood volume and pressure. The effect of external compression on vitreous and intraocular blood volumes has not been studied but a number of studies have been published on the effect of external compression on intraocular pressure and aqueous outflow facility.

The effect of eyelid blinking was studied by Miller (43). He found that normal blinking of the eye generated a transient increase in IOP of about 10 mm Hg, whereas a forceful blink generated an equally transient increase of 50 mm Hg. Similar results were reported by Coleman and Trokel (44). The effect of intermittent forceful eyelid squeezing on aqueous outflow facility was studied by Green and Lukenberg in volunteers with and without glaucoma (45). Forceful eyelid squeezing for 2 sec at 2-sec intervals was performed for 60 sec, and IOP and aqueous outflow facility were then calculated. Two types of responses were identified in the nonglaucomatous volunteers: responders, in whom IOP decreased significantly after the exercise, and nonresponders, in whom intraocular pressure changed minimally. In responders, IOP remained below control levels for several minutes. Responders had calculated values of total aqueous outflow facility greater than nonresponders. The outflow facility of nonresponders was similar to that of the glaucomatous patients after eyelid squeezing. The authors hypothesized that external compression increased aqueous outflow that resulted in a transient decrease in IOP.

Knowledge of the effects of external compression on increasing aqueous outflow led to the investigation of digital eyelid pressure as a therapeutic maneuver before intraocular surgery. Kirsch and Steinman (46) showed that digital pressure for 5 min before commencement of surgery significantly reduced IOP and thus increased the ease of surgery in patients for surgery under local anesthesia.

In a subsequent study, Kirsch studied the effect of differing the durations of digital pressure on the reduction of intraocular tension (47). He found that the greatest reduction in IOP occurred in the first minute of compression, but that further reduction in pressure occurred if digital compression was maintained over the next few minutes. He concluded that the optimal duration of digital pressure was about 5 min, after which time further compression had little effect.

Apart from the beneficial effect of digital pressure before intraocular surgery, the globe may be compressed before surgery through incorrect application of either an anesthetic mask prior to tracheal intu-

bation or surgical retractors to the eyelids, or through spasm of the extraocular muscles after succinylcholine administration. The effect of extraocular muscle spasm on intraocular pressure is dealt with below under the section dealing with neuromuscular blocking agents.

### Pharmacological Modification of Intraocular Pressure by Anesthetic Agents

IOP may be affected in a variety of ways by drugs given in the perioperative period by altering the above physiological determinants of IOP. They may act directly on the eye to induce changes in aqueous or intraocular blood volume; they may act locally by altering the tone of the extraocular muscles and thus alter external compression of the sclera, or they may act indirectly by altering vascular tone or central control of intraocular tension.

#### *Premedicants*

Diazepam has been used as a premedicant of special value in ophthalmologic surgery and as a means for prevention of succinylcholine-induced intraocular hypertension both orally and parenterally. The rationale behind the use of diazepam in ophthalmologic surgery is based on the belief that diazepam has centrally mediated muscle relaxing properties (48). Peripheral muscle relaxant effects have also been suggested (49,50).

Trew et al. (51) found that 0.2 mg/kg of diazepam given orally 90 min before induction of anesthesia had no effect on IOP, compared with a control group. However, when given intravenously just prior to induction of anesthesia, diazepam has been found to lower IOP (52-56). Al-Abrak was the first to describe this effect and found that 10 mg of diazepam given intravenously to unpremedicated adult patients without ocular disease significantly decreased IOP below control values (55). Pino-Capote studied the effect of diazepam given intravenously or into the conjunctival sac in decerebrate cats and found that diazepam by either route caused a significant decrease in IOP (54).

When used to attenuate the effects of succinylcholine on IOP, diazepam pretreatment has been found to be incompletely effective, causing some initial decrease in IOP but still allowing an increase in IOP above control values after succinylcholine administration (55,56).

The effect on IOP of neuroleptic agents given as premedicant drugs has not been well documented. The intraocular effects of these agents during maintenance of anesthesia using a neurolept technique has

received more attention. Presbitero et al. compared enflurane and neuroleptanesthesia using Innovar (57) in adult patients undergoing ophthalmic surgery. They found that with the neurolept technique a small but statistically insignificant increase in IOP occurred when stage I anesthesia was reached as assessed using a 16-channel EEG. Stages II and III were accompanied by statistically significant decreases in IOP below control levels. Ivankovic and Lowe (58) found a similar decrease in IOP with Innovar.

Morphine given intramuscularly to subjects with or without glaucoma decreases IOP (59). The effect of other opiates on IOP has not been studied but it is assumed they have a similar effect.

Anticholinergic drugs applied topically to the eye have significant effects on the eye; but when given intramuscularly as antisialogogic premedicants, they have no significant effects on intraocular tension (59-62). This has been shown for atropine, scopolamine, and glycopyrrolate.

#### *Induction Agents*

With the exception of ketamine, all of the agents commonly used to induce general anesthesia reduce IOP. Thiopental and pentobarbital, for example, significantly decrease IOP (32,52,63-66). It is believed that their main effect is the depression of the central controlling areas for IOP, although increased facility for aqueous drainage has also been shown to occur (32,66). Althesin, both for induction and maintenance of anesthesia, can reduce IOP to the same degree as thiopental (64).

The newer anesthetic induction agents have also been studied. Midazolam was compared with diazepam and thiopental by Fragen and Hauch and was found to reduce IOP to the same degree as the other two agents (52). As an induction agent, etomidate was found to reduce IOP significantly within 1 min of injection (67). When used for maintenance of anesthesia by continuous infusion at a rate of  $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , etomidate reduced IOP to a greater degree than did halothane anesthesia, when all other parameters were controlled (65).

Ketamine is a useful agent because it facilitates examination of the eyes in otherwise uncooperative children. Adams (68) compared the intraocular effects of ketamine (10 mg/kg intramuscularly) with halothane anesthesia in children and found that IOP was significantly higher with ketamine, a finding that agreed with earlier work by Harris et al. (69) and by Corssen and Hoy (70). Ketamine, because of these and other studies (71,72), is considered undesirable as an induction agent for intraocular surgery, but retains a

place as a useful agent for pediatric ophthalmological examination.

### *Inhalation Agents*

Inhalation anesthetics are thought to alter IOP in a number of ways: by an effect on the central controlling areas in the midbrain, by altering aqueous outflow facility, and by altering intra- and extraocular muscle tone.

Kornblueth et al. (32) studied the effect of diethyl ether, cyclopropane, and vinyl ether and found that all of these agents produced a depression of IOP of similar magnitude at equal depths of anesthesia. The depression in IOP was greater with increased depth of anesthesia irrespective of changes in blood pressure and respiration but correlated well with a measured increase in aqueous outflow facility. Chloroform, trichloroethylene, and halothane have similar effects (73). The effect of trichloroethylene on IOP is, however, somewhat controversial. Schreuder and Linssen (74) studied its effect in the monkey by placing a needle in the anterior chamber and directly measuring changes in pressure. They found that trichloroethylene increased IOP concurrently with an increase in CVP. Al-Abrak and Samuel (75) reported a similar effect in humans, when all other parameters were controlled. Adams et al. (76) reported a decrease in IOP with a lower (0.4%) concentration of trichloroethylene, but they noted that IOP tended to increase during the operation so that at the end of surgery IOP was not significantly different from preinduction levels. This, they stated, tended to confirm that trichloroethylene indeed increased IOP, and they recommended that concentrations greater than 0.4% should not be used for intraocular surgery.

The effect of nitrous oxide on IOP has received little attention even though today it is part of almost all commonly used anesthetic techniques. Intraocular injections of sulphur hexafluoride have recently been used in the treatment of giant retinal tears because it is absorbed more slowly from the eye than air. Wolf et al. (77) studied the effect of nitrous oxide on the size of such intraocular bubbles and noted that, because nitrous oxide is 117 times more soluble than sulphur hexafluoride and has a diffusion coefficient twice as great, a significant increase in bubble size and therefore IOP, could occur. They recommended that nitrous oxide be excluded from the anesthetic technique in patients in whom sulphur hexafluoride is injected intraorbitally.

The more modern volatile anesthetics decrease IOP in a dose-dependent manner, and few advantages have been attributed to one over another in this re-

gard. Halothane is usually the anesthetic against which others are compared. In spontaneously breathing patients, halothane reduces IOP by 18–33% (73,78,79). Enflurane reduces IOP by 21–40% in spontaneously breathing patients in concentrations of 1–5% (80,81). Isoflurane has been shown by Ansinsch, to reduce IOP from control values to the same degree as halothane, in a dose-dependent manner (82) compared with halothane at similar MAC concentrations in children.

It appears that the volatile agents are associated with dose-dependent reductions in IOP, but that factors such as  $PCO_2$  and posture may also play important roles in spontaneously breathing patients.

### *Neuromuscular Blocking Agents*

*Depolarizing (noncompetitive) agents.* The effect of succinylcholine on IOP is a result of the unique composition of extraocular muscles. Two distinct types of striated muscle fibers, twitch and slow fibers, have been demonstrated by functional studies in nonmammalian animal muscle (98). In 1963, Hess and Pilar (83) demonstrated morphologically and physiologically that the extraocular muscles of the cat had two such types of muscle fibers that differed from other types of muscle fibers. Anatomically one type of fiber, termed *Felderstruktur*, is large, irregular, and poorly defined, with multiple motor nerve endings of the "en grappe" type; the other type, termed *Fibrillenstruktur*, has a fibrillar pattern in which the fibrils are regular, distinct, and punctate, with a single motor nerve ending of the "n-plaque" type. Physiologically, two types of fibers were also demonstrated: a "twitch type" resulting in a rapid, transient contraction and a "tone type" resulting in slow, graded muscle contractions, accompanied by nonpropagated muscle potential of small amplitude and long duration. The relationship of "twitch type" fibers to *Fibrillenstruktur* and "tone type" to *Felderstruktur* has been demonstrated by Peachey and Huxley (84). Hess and Pilar (83) speculated about the physiological significance of the existence of two types of extrafusal muscle fibers in the eye when they had not been demonstrated elsewhere. They suggested that, whereas in other mammalian muscles "tonic" contractions appeared to be due to "twitch type" fibers with rather slow contraction times, the "twitch type" fibers of the extraocular muscles were so exceedingly fast that they might be unable to produce sustained smooth contraction. They therefore suggested that "twitch type" fibers may be necessary in the eye for rapid, scanning movement and that "tonic type" fibers are necessary to maintain steady binocular vision.



Two dose-dependent types of responses to succinylcholine have been demonstrated in the eye. Eakins and Katz (85) have suggested that these effects might relate to different effects on the two types of extraocular muscle fiber. They demonstrated that in anesthetized cats, "the intravenous injection of small doses of succinylcholine (less than 10  $\mu\text{g/kg}$ ) resulted in an increase in resting tension of the medial rectus muscle associated with an increase in twitch height. However, large doses of succinylcholine (30–150  $\mu\text{g/kg}$ ) produced a marked increase in resting tension as well as a severe reduction of the twitch response." They attributed "the increased muscle tension seen after the intravenous injection of succinylcholine to stimulation of the tonic system, and depression of the twitch response to blockade of the fast neuromuscular system." Subsequent work substantiated this and showed that pretreatment with *d*-tubocurarine could diminish the twitch response but had no effect on or sometimes increased the tonic response (86,87).

Apart from the effect of succinylcholine on extraocular extrafusal muscles, other mechanisms have been suggested to contribute to the effects of succinylcholine on the eye. Katz and Eakins (88,89) found that, even after sectioning of all of the extraocular muscles in the anesthetized cat, IOP was still elevated by succinylcholine. They suggested that succinylcholine produced its effect in part by increasing extraocular muscle tension and in part by contracting orbital smooth muscles, including "the retrobulbar muscle mass, arranged in bundles between the apex of the orbit and the posterior pole of the globe; the nictitating membrane and its muscle, which encircles the nasal one-third of the anterior half of the globe and intimately relates to the globe, and finally, smooth muscle elements attached to both lids." The mechanism by which succinylcholine causes orbital smooth muscle contraction in these studies is as yet unclear.

Clinical studies on the effect of succinylcholine on IOP confirmed earlier animal studies. Pandey et al. (90) studied the time-course of this effect and found that IOP was elevated 1 min after succinylcholine injection, was maximal at 2–4 min, and subsided at 6 min. They also found that tracheal intubation exaggerated but did not prolong this effect.

Different doses of succinylcholine have been studied in an attempt to confirm the work of Katz and Eakins in a clinical setting. Joshi and Bruce (91) gave 0.5 mg/kg or 1.0 mg/kg and found the higher dose caused less intraocular hypertension than the smaller. Cook (92), on the other hand, found that 1 mg/kg of succinylcholine caused a significant increase in IOP and that a higher dose (2.5 mg/kg) had a similar effect,

suggesting that the dose above the normal paralyzing dose was neither critical nor protective.

In an attempt to offset the potentially detrimental effects of succinylcholine in certain patients, a number of methods of pretreatment have been proposed, including small doses of competitive neuromuscular relaxants, "self taming" small doses of succinylcholine, and drugs such as hexafluorenum, acetazolamide, lignocaine, and diazepam.

Pretreatment with small doses of competitive neuromuscular blocking agents including gallamine, *d*-tubocurarine, pancuronium, and metocurine, have been recommended to reduce the elevation of IOP. The efficacy of such pretreatments in preventing the increase in IOP after succinylcholine is, however, disputed. In human studies, Miller et al. (93) found that pretreatment with 20 mg of gallamine or 3 mg of *d*-tubocurarine 3 min before succinylcholine administration, significantly attenuated the increase in IOP. Using similar methods, Bowen et al. (94) were unable to confirm this and found that no advantage was achieved with pretreatment. At present there are as many studies confirming as refuting the benefits of pretreatment with competitive neuromuscular blockers (93–97) as a means to prevent increases in IOP associated with succinylcholine.

"Self taming" involves the injection of subparalytic doses of succinylcholine (usually 10 mg in a 70 kg adult prior to administration of the paralyzing doses of succinylcholine with a view to desensitizing the neuromuscular junction to the subsequent, large dose. The benefits of "self taming" in attenuating the rise in IOP from succinylcholine is, however, like the competitive-blocker pretreatment, open to question. Verma (99) found that thiopental anesthesia reduced IOP and that pretreatment with succinylcholine (10 mg) elevated IOP to a level still below control values. A subsequent paralyzing dose of succinylcholine failed to further elevate IOP. Meyers et al. (100) used 0.2 mg/kg of succinylcholine as a "self taming" dose and found that IOP increased significantly above levels found before the "self taming" dose was given. A subsequent paralyzing dose of succinylcholine did not produce a further change in IOP. These authors concluded that succinylcholine with or without a "self taming" dose could not be recommended if any increase in IOP was to be prevented.

Pretreatment with other drugs has been recommended, but all have been shown to have limited success. Hexafluorenum has been shown by Katz et al. (101,102) to significantly attenuate the ocular hypertensive effects of succinylcholine in both cats and humans if given 1–2 min prior to succinylcholine

administration. Its effects included "a nondepolarizing blocking action, a plasma cholinesterase inhibiting effect and a junctional membrane effect," but the exact basis of its pretreatment effect remains unclear (102). When given with a longer interval between hexafluorenum and succinylcholine, the beneficial effect is lost. Sobel (103) also found that hexafluorenum fails to prevent the rise in IOP from succinylcholine, and Cullen (104) found that pretreatment with hexafluorenum made succinylcholine unsuitable for rapid sequence induction by inhibiting its paralyzing effects and thus negated any potential benefits conferred by hexafluorenum. Acetazolamide has also been used to inhibit the succinylcholine effect on IOP but with only limited benefit (105). Intravenous lidocaine (1–2 mg/kg) prior to succinylcholine has been shown similarly not to be completely effective (106). Intravenous diazepam decreases IOP but still allows an increase in IOP to a level above control values (55,56) after succinylcholine administration.

In conclusion, no method of pretreatment is consistently and completely effective in preventing the increase in IOP associated with succinylcholine administration.

*Nondepolarizing (competitive) agents.* The effect of *d*-tubocurarine on IOP has been the subject of many studies (32,88,107–109). A decrease in IOP of various degrees has been reported in almost all studies. This has been attributed mainly to a decrease in extraocular muscle tone but the concomitant decrease in systemic arterial pressure has also been implicated. Al-Abrak and Samuel (109) compared *d*-tubocurarine with pancuronium and found that *d*-tubocurarine produced a statistically significant depression of intraocular and systemic arterial pressure whereas, with an equipotent dose, pancuronium had no effect. They considered that the effect of *d*-tubocurarine may be due, not to an effect on extraocular muscle tone, but to its autonomic ganglion-blocking effect or to systemic arterial hypotension. Evidence to support this may also be found in the work of Katz and Eakins (88). They found evidence to suggest that neuromuscular blocking agents (succinylcholine and *d*-tubocurarine) act on both extraocular and intraocular muscles to produce their effects.

Studies of the effect of pancuronium on IOP have produced different results, probably as a result of differences in methods of evaluation and timing of measurements. George et al. (110) found that pancuronium caused no change in IOP. This is in agreement with the results of Al-Abrak and Samuel (109) but differs from results reported by Litwiller et al. (111)

and Smith and Leano (112). George et al. (110) premedicated their patients with morphine, diazepam, fentanyl, and droperidol and induced anaesthesia with thiopental. Orotracheal intubation was performed after local anesthetic (lidocaine) had been sprayed onto the larynx, and after steady-state conditions were reached, pancuronium or alcuronium was administered intravenously. Under these conditions, IOP was lower than awake values before administration of either neuromuscular blocking agent and did not change significantly after its injection. Litwiller et al. (111) gave pancuronium to anesthetized and unanesthetized subjects. In unanesthetized subjects 0.01 mg/kg of pancuronium decreased IOP to 80% of control at 2 min with a gradual return to control values by 8 min. In anesthetized subjects, thiopental decreased IOP, which then returned to normal within 6 min. A subsequent dose of pancuronium (0.08 mg/kg) produced another decrease in IOP to 70–84% of control after 1 min.

Alcuronium has been shown to have an effect similar to that of pancuronium on intraocular pressure at clinically used dosages (110,113,114).

Gallamine has been used in ophthalmic surgery mainly in an attempt to inhibit the increase in IOP occurring after succinylcholine administration. Initial work by Miller and Way showed that pretreatment with gallamine (20 mg) prevented this increase in IOP in both humans and cats (115). Subsequent studies by other investigators, however, failed to confirm these findings and some even showed a small increase in IOP in the pretreated groups (7,116,118).

Because of the rapidity of its action, fazadinium has been assessed as an alternative to succinylcholine for rapid sequence induction and intubation (119). The benefits of use of a nondepolarizing neuromuscular blocking agent for emergency ophthalmic surgery led to the investigation of fazadinium as a possible useful agent for such situations. Couch et al. (63) found that fazadinium did not increase IOP, which is consistent with the findings for other nondepolarizing agents, but neither did fazadinium afford any protection against the increase in IOP accompanying tracheal intubation. The authors concluded that fazadinium is an acceptable alternative to use of succinylcholine for emergency intraocular surgery.

Maharaj et al. (119) found that atracurium, one of the new nondepolarizing neuromuscular blocking agents, caused no change in IOP in patients under steady-state anesthesia. Vecuronium was studied by Sia and Rashkovsky (118) who measured IOP before and after induction of anesthesia with thiopental and 1, 3, and 5 min after tracheal intubation after 0.1 mg/kg

of vecuronium. In all cases, IOP decreased after thiopental and increased after intubation but never above preinduction levels. The authors considered vecuronium an acceptable drug for ophthalmic surgery.

## Conclusions

It is clear that many factors, both physiological and pharmacological, contribute to determine IOP during anesthesia. Probably the single most important factor, however, is the skill and experience of the anesthesiologist. A skillfully managed anesthetic is likely to have a more significant effect on operating conditions for eye surgery than any considerations of minor differences between pharmacological agents. Furthermore, the choice of anesthetic technique must consider factors other than intraocular pressure such as the patient's general condition and age, the nature and duration of the operation, and the skill of the surgeon. With regard to general anesthesia for patients with penetrating eye injuries, no clear and reliable methods for avoiding increases in IOP have been agreed upon. There is, as yet, no ultrarapidly acting nondepolarizing neuromuscular blocking agent to allow succinylcholine to be abandoned completely and no method of succinylcholine pretreatment is completely effective. For such surgery, the anesthesiologist must balance the overall risk to the patient with the risk to the injured eye, in deciding if succinylcholine is to be used. Even if an ultrarapidly acting nondepolarizing neuromuscular relaxant is found, the injured eye remains in danger from the ocular hypertensive effect of laryngoscopy and tracheal intubation. Unless the ocular hypertensive effect of laryngoscopy and tracheal intubation can be obtunded, any efforts to develop ultrarapidly acting nondepolarizing neuromuscular blocking agents will be in vain, at least in the area of emergency ophthalmic surgery.

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## Technical Communication

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# Effect of Halothane on Rat Liver Adenylate Cyclase: Role of Cytosol Components

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BERNSTEIN KJ, VEROSKY M, TRINER L. Effect of halothane on rat liver adenylate cyclase: role of cytosol components. *Anesth Analg* 1985;64:531-7.

*Halothane, in a number of tissues, alters the activity of adenylate cyclase, the enzyme that catalyzes the formation of cyclic 3',5'-adenosine monophosphate, an important intracellular regulator. The present studies demonstrate that in rat liver whole homogenates, basal and glucagon-stimulated adenylate cyclase activity is increased by halothane. In isolated rat liver membranes, halothane does not increase basal activity and it decreases activity stimulated by glucagon. Suspension of membranes in the cytosol fraction*

*restores the halothane-induced increase of basal and glucagon-stimulated activity. When cytosol denatured by trypsin or heat was used, the halothane-induced increase in glucagon-stimulated activity was lost, but the increase of basal activity was still observed. Suspension of membranes in albumin solution restored the effect of halothane on basal activity only. These results suggest the presence of heat-labile proteins in the cytosol fraction that modulate the halothane interaction with rat liver adenylate cyclase.*

**Key Words:** ANESTHETICS, VOLATILE—halothane. LIVER—adenylate cyclase. ENZYMES—adenylate cyclase.

In addition to its anesthetic effects on the brain, halothane has been shown to alter organ functions, including myocardial contractility, smooth muscle tone, platelet aggregation, and glucose metabolism in liver. In these organs, halothane induces a change in activity of adenylate cyclase, the enzyme that catalyzes the production of cyclic 3',5'-adenosine monophosphate (cAMP) from ATP (1-5). Cyclic AMP acts as a second messenger within cells, continuing the signal from hormones and neurotransmitters, the first messengers, located outside the cell. These hormones and neurotransmitters bind to specific receptors located on the outside of cells, activating adenylate cyclase and increasing the production of cAMP. In each of these organs, the halothane-induced change in adenylate cyclase activity and cAMP production is in the same direction as those which would lead to halothane-induced changes in function. This observation led us to hypothesize that these changes in function

were caused, at least in part, by halothane-induced changes in adenylate cyclase activity.

We recently reported that the halothane-induced depression of adenylate cyclase activity observed in whole homogenates of canine myocardium was lost when the adenylate cyclase-containing sarcolemmal membranes were isolated from other cellular components. The halothane effect was restored when sarcolemmal membrane was combined with a 100,000 × g supernatant fraction, which we call the cytosol fraction (1). The nature of the component in cytosol that restored the halothane effect in myocardial sarcolemmal membranes is unknown.

The studies presented here were performed in rat liver and were undertaken, first, to determine whether the effect of halothane on adenylate cyclase activity in liver membranes, in which halothane has a stimulatory effect, is dependent on cytosol components (as it is in myocardial sarcolemmal membranes, in which halothane has an inhibitory effect) and, second, to characterize the properties of such components. In the first experiments, the action of several concentrations of halothane on the activities of basal and glucagon-stimulated adenylate cyclase in liver whole homogenates was determined. The action of

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halothane on adenylate cyclase activity of a partially purified liver membrane preparation was then measured and the effect of the addition to the membranes of four modulators of adenylate cyclase, cytosol, glucagon, GTP, and halothane, alone and in combination, was determined. This was followed by measuring the halothane action on the adenylate cyclase of membranes suspended in undiluted and diluted cytosol, to assess the effect of dilution of cytosol components on the halothane effect. The effect of trypsin proteolysis and of heat denaturation, at 95 and 55°C, of cytosol components on halothane action on membrane adenylate cyclase was then measured. Finally, the effect on the halothane action of substituting exogenous protein for the cytosol components was determined by suspending membranes in albumin solution and measuring adenylate cyclase activity.

## Materials and Methods

### *Animals*

Male Sprague-Dawley rats, kept at 22°C on a 12-hr light/dark cycle and given Purina Rat Chow and water ad libitum until two hours before each experiment, were the source of livers used in these experiments. Each animal was stunned and decapitated; the liver was removed and immediately placed in iced 0.9% saline and then processed as follows.

### *Rat Liver Whole Homogenates*

Liver tissue was homogenized in 60 times its weight of 50 mM Tris buffer, pH 7.50, in a glass-pestle homogenizer at 4°C.

### *Rat Liver Membrane Preparations*

Membranes were obtained by a modification of the method previously described for the preparation of myocardial sarcolemma (1). The livers were obtained as described above, minced with scissors and homogenized in four volumes of 250-mM sucrose and 30-mM histidine buffer, pH 7.38, in a Polytron PT-10-ST tissue disrupter (Brinkmann Instruments, Inc, Westbury, NY) for 15-30 sec at a setting of 5. The homogenate was centrifuged at  $11,600 \times g$  for 20 min, and the supernatant was centrifuged at  $14,000 \times g$  for 20 min to remove connective tissue and heavy material. The resulting supernatant was centrifuged in a Beckman L5-40 ultracentrifuge (Beckman Instruments, Inc., Palo Alto, CA) at  $41,000 \times g$  for 30 min to produce a soft pellet that was separated by aspiration from its supernatant, which was used as de-

scribed below for the preparation of cytosol. The pellets were resuspended in sucrose-histidine buffer and centrifuged at  $100,000 \times g$  for 20 min. The resulting hard pellets, consisting of liver membranes, were separated from the supernatant by aspiration and resuspended in a volume of 1) sucrose-histidine buffer, 2) cytosol, full-strength or diluted, 3) trypsin-treated cytosol, 4) heat-treated cytosol, or 5) bovine serum albumin solution to make a membrane protein concentration of 5-9 mg/ml.

### *Cytosol Fraction Separation*

The supernatant of the  $41,000 \times g$  centrifugation was freed of remaining adenylate cyclase by centrifugation at  $100,000 \times g$  for 1 hr. The  $100,000 \times g$  supernatant was collected and called the cytosol fraction.

### *Trypsin Treatment of Cytosol*

Proteolytic degradation of cytosol components was accomplished by incubating an aliquot of the cytosol fraction with trypsin (bovine pancreatic) 1 mg/ml in the presence of 5-mM  $MgSO_4$  for 20 min at 37°C. The reaction was stopped by the addition of soya trypsin inhibitor (final concentration 2 mg/ml) (6). The mixture was then centrifuged at  $1300 \times g$  for 10 min. The supernatant was used as trypsin-treated cytosol fraction.

### *Heat Treatment of Cytosol*

Denaturation of cytosol components by heat was accomplished by placing an aliquot of the cytosol fraction in a bath at 55 or 95°C for 10 min, followed by centrifugation at  $50,000 \times g$  for 10 min (6). The supernatant was the source for 55°C-treated or 95°C-treated cytosol fraction.

### *Albumin Solution*

Membrane pellets were suspended in an 11.8 mg/ml solution for bovine albumin. This albumin concentration was the same as the average protein concentration of the cytosol fraction.

### *Measurement of Adenylate Cyclase Activity*

Adenylate cyclase activity was determined by measuring the conversion of exogenous [ $\alpha$ - $^{32}P$ ]-ATP to [ $^{32}P$ ]-cAMP in the presence of 1-mM ATP, 3 mM  $MgSO_4$ , with both an ATP regenerating system, consisting of pyruvate kinase (15  $\mu$ g/ml) and 3.3 mM phosphoenolpyruvate, as well as an excess of cAMP

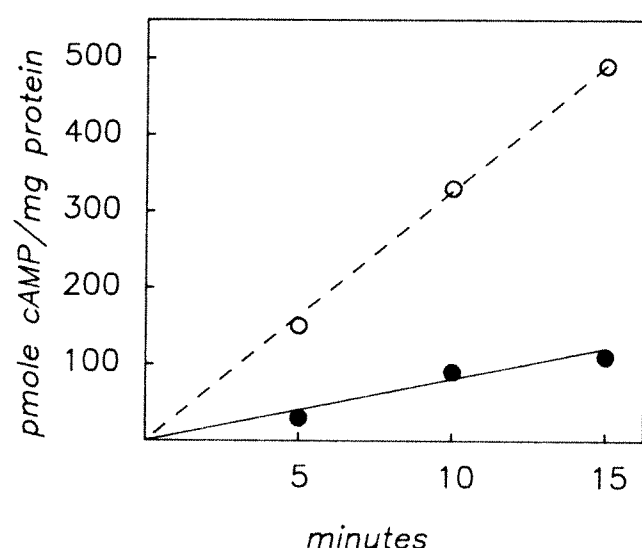


Figure 1. Adenylate cyclase activity in rat liver whole homogenates is expressed as pmole cAMP produced per mg protein. Data are from a representative experiment. Solid line represents basal activity. Dashed line represents activity in the presence of 1- $\mu$ M glucagon.

(5 mM) to minimize breakdown of labeled cAMP by phosphodiesterase. Then 100  $\mu$ l of the above incubation mixture with an appropriate volume of 50 mM Tris buffer, pH 7.5, was flushed for 20 min with halothane in humidified oxygen, delivered from an Ohio anesthesia machine with a Verni-trol vaporizer (Ohio Medical Products, Madison, WI) via a metal and polyethylene manifold. In some experiments, glucagon (10  $\mu$ M), or guanosine triphosphate (GTP) (100  $\mu$ M), or both, was also added to the incubation mixture and the reaction tubes were placed in a 30°C water bath with vapor flush continued. Each incubation measuring the effect of 3, 5, or 7% halothane in whole homogenates was performed with homogenates from the same rat. The conversion of ATP to cAMP was begun by the addition of 75  $\mu$ l of tissue sample (final volume of incubation mixture: 300  $\mu$ l) and stopped after 15 min by addition of 100  $\mu$ l of 2.67N perchloric acid. Control samples flushed with oxygen alone were incubated in the same manner.

The [ $^{32}$ P]-cAMP was isolated by double column ion-exchange chromatography using Dowex 50W-X8 and alumina, WH-3 neutral, in 0.25  $\times$  2.25- and 0.25  $\times$  1.75-inch columns, respectively (7). Isolated [ $^{32}$ P]-cAMP was measured by liquid scintillation spectrometry (Packard TRI-CARB 460, Packard Instrument Co, Inc, Downers Grove, IL) in Bray's solution with recovery of cAMP measured by ultraviolet spectrophotometry (Gilford 240, Gilford Instrument, Oberlin, OH) at 259 nm.

Table 1. Effect of Halothane on Adenylate Cyclase Activity in Rat Liver Whole Homogenates

	Basal activity	Net glucagon stimulation
Control	49.2 $\pm$ 6.8	245.7 $\pm$ 31.8
Halothane 3%	55.1 $\pm$ 7.0	278.3 $\pm$ 27.4
Difference	5.9 $\pm$ 1.2 <sup>a</sup>	32.6 $\pm$ 5.5 <sup>a</sup>
Control	50.1 $\pm$ 5.6	249.3 $\pm$ 25.3
Halothane 5%	62.8 $\pm$ 7.7	295.3 $\pm$ 31.4
Difference	12.7 $\pm$ 2.8 <sup>a</sup>	46.0 $\pm$ 10.3 <sup>a</sup>
Control	55.6 $\pm$ 3.7	232.7 $\pm$ 17.9
Halothane 7%	79.8 $\pm$ 9.0	320.0 $\pm$ 20.1
Difference	24.2 $\pm$ 8.5 <sup>a</sup>	87.3 $\pm$ 21.6 <sup>a</sup>

Adenylate cyclase activity is expressed as pmole cAMP produced per mg protein per 15 min. Values are means  $\pm$  SEM. For 3 vol% experiments,  $n = 5$ ; for 5 and 7 vol% experiments,  $n = 6$ . Significance is tested by paired  $t$ -test.

<sup>a</sup>Effect is significant ( $P < 0.05$ ).

Protein concentrations were determined by the method of Lowry et al. (8). The activity of adenylate cyclase is expressed as pmole cAMP formed per mg protein. All determinations were performed in triplicate.

Statistical significance was tested by Student's  $t$ -test for paired data, two-way analysis of variance with multifactorial analysis using a Yates' algorithm for multifactorial experiments (9) and factorial analysis using a multiple-regression approach for estimation of parameters. Results were considered significant when  $P < 0.05$ .

The [ $\alpha$ - $^{32}$ P]-ATP was obtained from the Amersham Corp; ATP, GTP, phosphoenolpyruvate, and pyruvate kinase from the Boehringer-Mannheim Corp; cAMP, glucagon, trypsin, soya trypsin inhibitor, and WH-3 alumina (neutral form) from the Sigma Chemical Corp; Dowex 50W-X8 ion exchange resin from the Baker Chemical Co; and halothane (Fluothane) from Ayerst Laboratories Inc.

## Results

### Whole Homogenate

Basal and 1  $\mu$ M glucagon-stimulated adenylate cyclase activities were linear with time to 15 min at 30°C (Fig. 1). Halothane 3, 5, and 7 vol% caused concentration-dependent increases in basal (12, 25, and 44%, respectively) adenylate cyclase activity and in net stimulation of adenylate cyclase by glucagon (13, 18, and 38%, respectively) (Table 1).

### Membrane Preparation

Basal adenylate cyclase activity, as well as activities stimulated by 10- $\mu$ M glucagon and 100- $\mu$ M GTP, alone



**Table 2.** Effect of Suspension Medium and Halothane on Rat Liver Membrane Adenylate Cyclase Activity

	Cytosol	Buffer
Control		
(Basal)	37.1 ± 4.1	88.9 ± 6.2
Glucagon 10 $\mu$ M	169.9 ± 19.5	427.2 ± 21.4
Glucagon plus GTP 100 $\mu$ M	167.4 ± 15.1	462.5 ± 25.0
GTP	40.9 ± 5.4	120.5 ± 6.1
Halothane 5 vol%		
(Basal)	44.2 ± 4.8	86.4 ± 3.7
Glucagon 10 $\mu$ M	225.9 ± 18.0	388.6 ± 18.0
Glucagon plus GTP 100 $\mu$ M	216.6 ± 16.4	400.9 ± 15.9
GTP	48.0 ± 5.0	118.0 ± 4.5

Adenylate cyclase activity is expressed as pmole cAMP produced per mg membrane protein per 15 min. Values are means  $\pm$  SEM;  $n = 5$ . *Control* and *(basal)* indicate the absence of halothane and glucagon, respectively. Data were analyzed by two-way analysis of variance for four factors at two levels. Factor(s) or interaction(s) are considered significant at  $P < 0.05$ . Significant factor(s) and interaction(s) are as follows: glucagon, GTP, cytosol, halothane plus cytosol, glucagon plus cytosol, halothane plus glucagon + cytosol.

and in combination, were linear with time to 15 min in membranes suspended either in buffer or in the cytosol fraction (data not shown). These activities were similar to the results of others (10,11).

In a series of experiments comparing adenylate cyclase activities of membranes suspended in cytosol or sucrose-histidine buffer, 10- $\mu$ M glucagon stimulated adenylate cyclase of membranes suspended in either buffer or cytosol, although 100- $\mu$ M GTP increased activity only when buffer was the suspension medium. Glucagon stimulation was not enhanced by the addition of GTP to membranes suspended in either medium. In membranes suspended in buffer, halothane had no effect on basal or GTP-stimulated activities, but decreased activity stimulated by glucagon (by 9%) or by glucagon with GTP (by 13%). In membranes suspended in cytosol, halothane increased basal activity (by 19%) and activities stimulated by either glucagon (33%) or GTP (17%) alone and in combination (29%). Analysis by Yates' algorithm for a multifactorial study using a two-way analysis of variance shows significant effects by single factors and interactions of factors (Table 2). Thus the suspension medium had two major effects on adenylate cyclase activity. Membranes suspended in cytosol had markedly decreased basal activity and net stimulation of adenylate cyclase by glucagon compared to membranes suspended in buffer. In addition, whereas halothane decreased net glucagon stimulation of adenylate cyclase in membranes suspended in buffer, halothane increased net glucagon stimulation in membranes suspended in cytosol.

**Table 3.** Effect of Trypsin Treatment of Cytosol on Halothane Alteration of Rat Liver Membrane Adenylate Cyclase Activity

	Untreated cytosol	Trypsin-treated cytosol
Control: (basal)	42.1 ± 3.0	144.2 ± 22.7
Halothane 5 vol% (basal)	49.1 ± 3.5	182.7 ± 10.1
Control: glucagon 10 $\mu$ M	193.9 ± 14.8	352.3 ± 17.3
Halothane plus glucagon	244.1 ± 19.8	328.9 ± 15.7

Adenylate cyclase activities are expressed as pmole cAMP produced per mg membrane protein per 15 min. Values are means  $\pm$  SEM;  $n = 7$ . *Control* and *(basal)* indicate the absence of halothane and glucagon, respectively. Data were analyzed by two-way analysis of variance for three factors at two levels. Factor(s) or interaction(s) are considered significant at  $P < 0.05$ . Significant factor(s) and interaction(s) are as follows: halothane, glucagon, trypsin-treated cytosol, and halothane plus glucagon plus trypsin-treated cytosol.

### Dilution Studies

Membranes were suspended in full-, half-, or quarter-strength cytosol or in buffer, and glucagon-stimulated adenylate cyclase activity was measured in the absence and presence of 5 vol% halothane. As in the results listed above, suspension of membranes in full-strength cytosol fraction decreased glucagon-stimulated activity. Halothane caused significant increases in glucagon-stimulated activity in membranes suspended in full-strength and half-strength cytosol (Fig. 2).

### Trypsin Denaturation Studies

Basal and glucagon-stimulated activities were significantly higher in membranes suspended in trypsin-treated cytosol than in untreated cytosol. Halothane caused 17 and 28% increases in basal and net glucagon-stimulated activities in membranes suspended in untreated cytosol and a 27% increase in basal activity and a 30% decrease in net glucagon stimulation in membranes suspended in trypsin-treated cytosol (Table 3).

### Heat-treatment Studies

Basal and glucagon-stimulated adenylate cyclase activities in membranes suspended in cytosol heated to 55 and 95°C for 10 min were significantly higher compared with membranes suspended in untreated cytosol. Halothane increased basal activity in membranes suspended in untreated cytosol and, to a smaller extent, in 55°C-treated cytosol. The halothane-induced increase in net stimulation by glucagon observed in membranes suspended in untreated cytosol was abolished by 55°C- and 95°C-treatment of cytosol (Table 4).

**Table 4.** Effect of Heat Treatment of Cytosol on Halothane Alteration of Rat Liver Membrane Adenylate Cyclase Activity

	Untreated cytosol	95°C treatment	55°C treatment
Control: (basal)	44.4 ± 2.2	142.9 ± 20.0	60.7 ± 7.8
Halothane 5 vol% (basal)	52.3 ± 2.7	133.9 ± 11.5	66.9 ± 6.4
Control: glucagon 10 µM	212.3 ± 12.1	389.0 ± 20.9	350.4 ± 27.7
Halothane plus glucagon	266.1 ± 15.9	362.7 ± 16.9	339.6 ± 15.0

Adenylate cyclase activity is expressed as pmole cAMP produced per mg membrane protein per 15 min. Values are means ± SEM; *n* = 11. Data were analyzed by factorial analysis using a multiple regression approach. Factor(s) or interaction(s) are considered significant at *P* < 0.05. Significant factor(s) and interaction(s) are as follows: heat-treated cytosol, glucagon, heat-treated cytosol plus glucagon, and heat-treated cytosol plus halothane.

### Albumin Substitution Studies

Basal and glucagon-stimulated activities were significantly higher in membranes suspended in albumin solution compared with membranes suspended in the cytosol fraction (Table 5). Halothane induced 24 and 19% increases in basal activity in membranes suspended in cytosol and albumin solution. Halothane also induced an 18% increase in net stimulation by glucagon in membranes suspended in cytosol and no change in membranes suspended in albumin solution.

### Discussion

The functional changes induced by halothane in many tissues are accompanied by alterations in adenylate cyclase activities. Of special interest to anesthesiologists is the relaxant effect of halothane on smooth muscle (3), associated with increases in adenylate cyclase activity, and the depressant effect of halothane on cardiac muscle (1,2), associated with decreases in adenylate cyclase activity. In liver, halothane increases glycogenolysis with a decrease in glycogen content and an increase in blood glucose concentration (12). Glucagon and epinephrine cause similar effects in liver through stimulation of adenylate cyclase and increases in intracellular cAMP. Thus we hypothesize that the effect of halothane on liver glycogen metabolism is mediated through stimulation of adenylate cyclase.

The results of our experiments demonstrate that the halothane-induced increase in basal and glucagon-stimulated adenylate cyclase activity is concentration-dependent in whole homogenates of rat liver and comparable to the results of others (4). The halothane effect on liver adenylate cyclase is also similar

**Table 5.** Effect of Albumin Substitution for Cytosol on Halothane Alteration of Rat Liver Membrane Adenylate Cyclase Activity

	Untreated cytosol	Albumin solution
Control: (basal)	56.1 ± 4.0	80.7 ± 9.7
Halothane 5 vol% (basal)	69.8 ± 7.0	96.0 ± 9.5
Control: glucagon 10 µM	250.2 ± 12.8	329.3 ± 17.9
Halothane plus glucagon	299.2 ± 14.3	345.5 ± 19.4

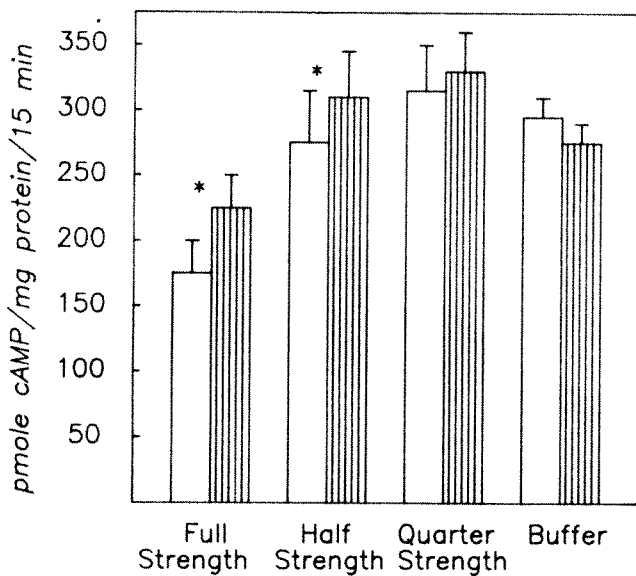
Adenylate cyclase activity is expressed as pmole cAMP produced per mg membrane protein per 15 min. Values are means ± SEM; *n* = 8. Control and (basal) indicate the absence of halothane and glucagon, respectively. Data were analyzed by two-way analysis of variance for three factors at two levels. Factor(s) or interaction(s) are considered significant at *P* < 0.05. Significant factor(s) and interaction(s) are as follows: halothane, albumin, glucagon, albumin plus glucagon.

to the halothane effect on the enzyme in rat uterus (3), rat caudate nucleus (13), and human platelets (5). Our present results show that this effect of halothane is dependent on certain cytosol factors.

Adenylate cyclase activity of liver membranes separated from other cellular components was significantly greater when suspended in buffer than in cytosol, suggesting the presence of inhibitory components in cytosol. Similar inhibitory factors in rat liver cells have been postulated previously (14). Our dilution studies indicate that the action of the inhibitory component is concentration-dependent (Fig. 2), an observation comparable to the results reported in the literature (10). Denaturation of the cytosol by proteolysis (Table 3) indicated that the component is protein in nature. Treatment of the cytosol by heat at 55 and 95°C (Table 4) resulted in increases of adenylate cyclase activities, indicating that this inhibitory component is relatively but not absolutely heat-stable. Both basal and glucagon-stimulated activities were higher in membranes suspended in an albumin solution of the approximate protein concentration of cytosol than in cytosol itself (Table 5), indicating that this inhibitory component cannot be mimicked by exogenous random proteins.

The higher basal adenylate cyclase activities of membranes suspended in trypsin or 95°C-treated cytosol than in buffer suggest a second, stimulatory, component in cytosol. The activation by such a component seems to be unmasked only when the inhibitory component is not present (10). One such possible endogenous modulator previously identified in the cytosol fraction, also heat-stable and resistant to proteolysis, is GTP.

The effect of halothane on adenylate cyclase was significantly affected by the medium in which membranes were suspended. Halothane increased basal and stimulated adenylate cyclase activities in mem-



**Figure 2.** Action of halothane on adenylate cyclase of rat liver membranes suspended in full-, half-, or quarter-strength cytosol or buffer. Activities are in the presence of  $10\text{-}\mu\text{M}$  glucagon and are expressed as pmole cAMP produced per mg membrane protein per 15 min. Values are means  $\pm$  SEM. Open bars represent control. Hatched bars represent halothane 5 vol%. Data were analyzed by paired *t*-tests;  $n = 5$ . (\*, Difference is significant at  $P < 0.05$ .)

branes suspended in cytosol, as it did in whole homogenates. In contrast, halothane had no effect on basal and GTP-stimulated adenylate cyclase activities and even decreased glucagon-stimulated activity in membranes suspended in buffer (Table 2). Furthermore, dilution of the cytosol proportionately decreased the effect of halothane on glucagon stimulation (Fig. 2).

The halothane-induced enhancement of glucagon-stimulated adenylate cyclase activity observed in membranes suspended in cytosol was abolished by trypsin or heat treatment of the cytosol at either  $55$  or  $95^{\circ}\text{C}$ , indicating that the cytosol component that promotes the halothane effect is a heat-labile protein. In contrast, the stimulatory effect of halothane on basal activity in membranes suspended in cytosol was still evident after trypsin (Table 3) and  $55^{\circ}\text{C}$  pretreatment, and it was abolished only with  $95^{\circ}\text{C}$  pretreatment, the only treatment that caused the precipitation of virtually all protein from the cytosol (Table 4). In addition, this halothane effect was preserved in membranes suspended in albumin, although the halothane-induced increase in net glucagon stimulation was absent (Table 5). The cytosol component that promotes halothane stimulation of basal activity, therefore, can be mimicked by other protein molecules. The similar effects of dilution, heat treatment and proteolysis of cytosol on both glucagon-stimulated

adenylate cyclase and halothane-induced increase of glucagon stimulation suggest that a single component is possibly involved in both effects.

There are questions to be answered about the interaction of halothane and adenylate cyclase. How does halothane alter adenylate cyclase activity and why does it stimulate adenylate cyclase under some circumstances and depress it in others? We have shown previously that halothane has no effect on receptor binding properties in myocardial membranes (15), and we currently believe its mode of action may involve nucleotide binding units that remain attached to the membranes during their preparation. At present, it is commonly believed that the adenylate cyclase complex consists of three types of units: a regulatory unit with hormone-binding receptors on the outside of the plasma membrane that can combine with a nucleotide binding unit when the receptor is occupied by an agonist. The nucleotide binding unit is so named because it binds the guanine nucleotides GTP and guanosine diphosphate (GDP), controlling the activity of the catalytic unit that catalyzes the conversion of ATP to cAMP. It has become evident that there are two types of nucleotide binding units associated with most adenylate cyclases: those that promote stimulation by such molecules as glucagon and  $\beta$ -adrenergic agonists, and those that promote inhibition, by such molecules as  $\alpha$ -adrenergic and muscarinic cholinergic agonists (16). Halothane might functionally alter either type of nucleotide binding unit or their interaction with certain cytosol components and thus alter adenylate cyclase activity. Such a hypothesis could account for the different effects of halothane on adenylate cyclase in liver membranes in the absence and presence of cytosol, as well as in different tissues.

In conclusion, we have shown that in liver the effect of halothane on adenylate cyclase activity is dependent on the presence of the cytosol fraction. Our results indicate that the component in cytosol on which the effect of halothane depends is a heat-labile, water-soluble protein and that the degree of the effect depends on the amount of component present.

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## Clinical Reports

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### Adjunctive Use of Dantrolene in Severe Tetanus

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Despite a high rate of tetanus immunizations in the United States, sporadic cases of tetanus continue to be encountered, especially in the elderly (1). The management of severe tetanus includes wound debridement, administration of antibiotics, passive immunizations with human antitoxin and the securing of an adequate airway. Spasmolytics, neuromuscular blocking agents, and mechanical ventilation are usually required in conjunction with nutritional and psychological support (2). The ideal spasmolytic agent for use in tetanus would produce relaxation of skeletal muscles, have little effect on the level of consciousness, leave ventilation unimpaired and be free of stimulatory cardiovascular side effects. Dantrolene sodium is a direct acting muscle relaxant and has the advantage of minimal CNS depression. We report the adjunctive use of this agent in severe tetanus occurring in a previously unimmunized man.

#### Case Report

A 30-yr-old Mexican man was admitted to the Ventura County Medical Center in December 1983, four days after sustaining a puncture wound from a rusty carpenter's nail. Twenty-four hours before admission, the patient experienced progressive tightness of his jaw together with pain and stiffness in the shoulders and back. Past medical history was unremarkable other than he had not received prior tetanus immunizations. He had recently immigrated to California from Mexico.

Physical examination revealed an intelligent, pleasant, and muscular man who was mildly anxious. His blood pressure was 160/90 mm Hg. His temperature

was 36.8°C, pulse rate was 68, and respiration rate was 18 breaths/min. There was marked trismus; and risus sardonicus was noted. His neck and back were held in rigid extension. The chest was clear to auscultation. The heart was normal to auscultation; the abdomen was soft and nontender without masses or organomegaly. Examination of the extremities revealed a 1–2 mm puncture wound on the distal plantar aspect of the right foot without surrounding erythema, tenderness, or swelling. The neurologic examination was unremarkable except for the muscular rigidity. The remainder of the physical examination was normal.

His white blood cell count was 10,100 mm<sup>3</sup> with 74 segmented forms and 19 lymphocytes. The hemoglobin was 16.2 g. Serum electrolyte levels, including calcium, were normal, as was urinalysis, the electrocardiogram, and a chest x-ray. A diagnosis of tetanus was made and the patient was given 3000 units of tetanus-immune globulin intramuscularly. Two-million units of penicillin G were administered intravenously every 4 hr for 9 days.

Within a few hours of admission and despite the use of intravenous diazepam, abdominal rigidity ensued. Painful myoclonus occurred with mild stimulation. An elective tracheostomy was performed. Within 24 hr of admission, opisthotonos occurred, requiring a constant infusion of pancuronium bromide (3–4 mg/hr) and the institution of mechanical ventilation, both of which were continued for the succeeding 14 days. Morphine sulfate and diazepam were employed for sedation.

The course of the patient's illness was complicated by sustained hypertension and tachycardia due to tetanus, pancuronium, or perhaps both, which were easily managed with hydralazine and propranolol. On the twelfth hospital day, fever occurred that was due to *Serratia* urinary tract infection and *Pseudomonas aeruginosa* pneumonia. Both resolved with antibiotic ther-

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apy. Total parenteral nutrition was initiated on the ninth hospital day after failure of repeated attempts at enteral alimentation.

To assess the ongoing need for neuromuscular blockade, pancuronium was discontinued on the fifteenth hospital day with the almost immediate return of diffuse muscular spasm. Dantrolene sodium, 140 mg (1.5 mg/kg), was then given as an intravenous bolus. Paroxysms of muscular spasm resolved, although spasms could be induced by tactile stimulation. Dantrolene, 1 mg/kg, was continued intravenously every 4 hr for 24 hr. Soon thereafter, the patient was able to nod in response to questioning and to move his upper extremities on command.

On the next day oral dantrolene, 100 mg every 4 hr, was begun via nasogastric tube and increased after 12 hr to 150 mg every 4 hr. Thereafter an occasional supplemental intravenous dose of dantrolene was required to control induced spasms.

Enteral alimentation was again attempted and was successful. The patient had progressively greater active range of motion and by the twenty-ninth hospital day, he could actively move to a wheelchair and stand unassisted. There were continued spasms of his lower extremities with voluntary movement, but these gradually regressed, and by the time of discharge on the thirty-sixth hospital day, he could ambulate with some assistance. The patient continued to receive physical therapy on an outpatient basis over the succeeding four weeks, at which time he was discharged from further treatment without residual impairment.

## Discussion

The most frequent complications associated with severe tetanus treated by modern methods of muscle relaxants and artificial ventilation include pulmonary embolism and septic complications associated with long-term mechanical ventilation and indwelling urinary and intravenous catheters (3). An agent that would obviate or shorten the duration of paralysis and mechanical ventilation would represent an advance in the management of this disease.

The centrally acting myorelaxant diazepam is effective in mild and moderately severe forms of tetanus (4-7). It has an adjunctive role in severe disease when combined with direct-acting relaxants, such as pancuronium or curare, by providing sedation and amnesia.

Dantrolene sodium is a direct-acting muscle relaxant that has been effective in the management of malignant hyperthermia (8,9) and the neuroleptic malignant syndrome (10). This drug has been used most commonly in the management of spasticity compli-

cating spinal cord injury, stroke, and multiple sclerosis (11). Dantrolene is believed to exert its action at the site of muscle contraction, reducing the influx of calcium into sarcoplasm and thereby inhibiting excitation-contraction coupling (12).

Rocha (13) reported the use of orally and rectally administered dantrolene in the convalescent phase of tetanus in 21 patients. He noted a clear relaxant effect with reduction of trismus and decreased intensity of spasm. Similar findings were noted in a case report by Ortega Cerda et al. (14).

The patient reported here had generalized muscle spasms of such intensity that effective ventilation was impossible without use of a constant infusion of 3-4 mg/hr of pancuronium. When pancuronium was discontinued on the fifteenth hospital day, muscle spasms and opisthotonos recurred. There was, however, a dramatic clinical response to intravenous dantrolene. Although diffuse spasms could be provoked by stimulation initially, these soon abated with continued use of dantrolene. Gastric paresis, presumably related to pancuronium (15), resolved once dantrolene was substituted, allowing enteral alimentation. After dantrolene, spontaneous respirations resumed, and the patient could be weaned from assisted ventilation. Within 24 hr he was able to communicate and actively participate in his care.

The dosage of dantrolene we employed was considerably higher than those reported by Rocha (13) or Ortega Cerda et al. (14). After the initial doses, subsequent intravenous and oral doses were determined by the control of symptoms. Oral dantrolene was tapered during the patient's convalescence as determined by the presence of muscle rigidity. Dantrolene appears to have been well tolerated. There were mild elevations of serum levels of hepatic transaminases and a marked increase in the alkaline phosphatase. The exact temporal relationship of these enzyme elevations and drug administration is, unfortunately, not clear. However, laboratory values returned to normal ranges once the drug was discontinued. Although dantrolene is known to cause hepatotoxicity when given orally for prolonged courses (11), we are unaware of toxicity studies in humans employing high-dose intravenous or oral dantrolene for short periods. No other adverse effects were noted.

The place of dantrolene in the management of tetanus is uncertain. From the limited experience reported here, the drug was clearly efficacious in the latter part of this man's severe illness. It would be of great clinical interest and importance to evaluate the use of dantrolene in mildly and moderately ill patients with tetanus, and to cautiously employ it early in the management of severe disease. Objective measure-

ments of muscle relaxant effects correlated with dantrolene blood levels and serum level of hepatic transaminases would be valuable and should be part of future clinical investigations.

In summary, neuromuscular blockade and mechanical ventilation were required in the management of this 30-yr-old man with severe tetanus. Dantrolene sodium was substituted for pancuronium and was efficacious in controlling severe muscle spasm. Dantrolene appears to be an effective adjunct to neuromuscular blocking agents and may prove to be effective as a single agent in mild to moderate tetanus.

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## Positive End-Expiratory Pressure Produced by Water in the Condensation Chamber of a CO<sub>2</sub> Absorber

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Anesthetic morbidity and mortality can be attributed to both human error and equipment malfunction. For example, Cooper et al. (1) found that 82% of preventable anesthetic mishaps involved human error while only 14% involved overt equipment malfunction. The remaining 4% involved both human error and equipment malfunction. The most frequent human errors involved problems with ventilation and breathing circuits.

### Case Report

Recently we observed a case involving human error (failure to drain CO<sub>2</sub> absorber) in which positive end-expiratory pressure (PEEP) was inadvertently produced in the anesthesia breathing circuit when water accumulated in the condensation chamber at the bottom of the carbon dioxide absorber (Foregger model CF-4 Jumbo Absorber). In this case, 10-cm H<sub>2</sub>O pressure was recorded on the breathing circuit pressure manometer (expiratory path) at the end of expiration in a semiclosed circle system (Foregger anesthesia machine model LICH) during mechanically controlled ventilation of the lungs. The level of PEEP persisted despite disconnecting either the waste anesthetic gas scavenging system or the ventilator from the circle breathing system. This eliminated mechanical malfunction of these components (particularly faulty unidirectional or pop-off valves) as causes of the problem. Next, the inspiratory and expiratory breathing hoses of the circle system were inspected for the presence of water because a heated humidifier was being used. Despite draining approximately 20 ml of water from the expiratory hose, the level of PEEP (10-cm H<sub>2</sub>O) remained unchanged. Similarly, disconnecting the breathing circuit from the endotracheal tube did

not correct the problem. At this time gurgling sounds could be heard from the CO<sub>2</sub> absorber, suggesting that this might be the source of the problem. Indeed, opening the drain plug at the bottom of the condensation chamber of the CO<sub>2</sub> absorber resulted in the removal of about 250 ml of water and the elimination of the 10-cm H<sub>2</sub>O PEEP from the circle breathing system. No adverse hemodynamic responses were produced by the 10-cm H<sub>2</sub>O PEEP.

### Methods

We then decided to investigate this observation by adding water in known amounts to the condensation chamber of ten different freshly packed CO<sub>2</sub> absorbers (Foregger model CF-4) during mechanically controlled ventilation of the lungs of ten different patients. End-expiratory and peak inspiratory (PIP) proximal airway pressures were measured at the endotracheal tube connection to the circle breathing system. In addition, the volume of water that occluded the opening of the outlet tube of the condensation chamber was measured. Finally, a CO<sub>2</sub> absorber was modified by replacing the metal tube connecting the outlet of the condensation chamber to the inspiratory valve with rigid translucent tubing in order to measure the vertical column of water producing the PEEP. Data were analyzed by two-way analysis of variance followed by Dunnett's test, and  $P < 0.05$  was considered statistically significant. All procedures followed in this study were in accord with the ethical standards of the Committee on Human Experimentation.

### Results

Data are illustrated in Fig. 1. Water volumes in the condensation chamber less than 175 ml produced no significant change in PEEP measurements above the baseline 2–3-cm H<sub>2</sub>O value produced by the ventilator pop-off valve. However, water volumes exceeding 200 ml resulted in PEEP values significantly greater than baseline values. Indeed, water volumes of 250 ml

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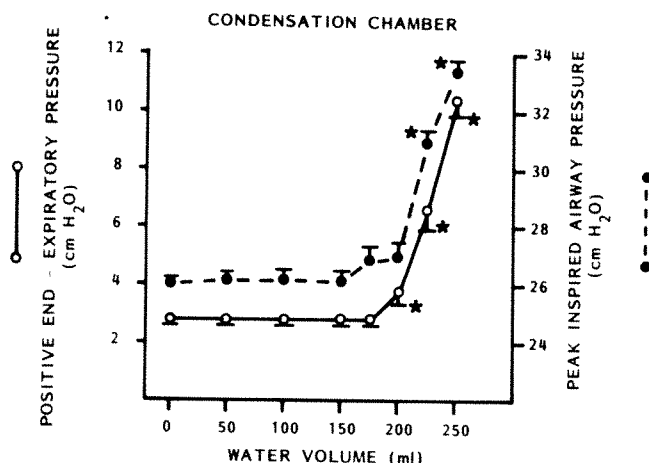


Figure 1. Positive end-expiratory and peak inspiratory airway pressures measured in cm H<sub>2</sub>O produced by incremental volumes of water added to the condensation chambers of 10 different CO<sub>2</sub> absorbers. Values are mean  $\pm$  SEM. (\* indicates significant difference,  $P < 0.05$ , between value indicated and value measured at 0 chamber water volume).

produced PEEP values in excess of 10-cm H<sub>2</sub>O. Likewise PIP increased significantly from 26- to 33.5-cm H<sub>2</sub>O (30% increase) when the water volume in the condensation chamber increased from volumes less than 200 ml to 250 ml. The magnitude of increase in PIP (7.5-cm H<sub>2</sub>O) was less than the increase in PEEP (10-cm H<sub>2</sub>O). The volume of water in the condensation chamber that just occluded the opening to the metal tube that carries gas out of the CO<sub>2</sub> absorber measured approximately 200 ml. In the modified CO<sub>2</sub> absorber, a column of water in the clear vertical tube connecting the outlet of the condensation chamber to the inspiratory valve measured 10-cm high when end-expiratory proximal airway pressure measured 10-cm H<sub>2</sub>O (G in Fig. 2). No adverse hemodynamic or ventilatory effects were observed in any patient.

## Discussion

This case study demonstrated that PEEP can be inadvertently produced by water accumulating in the condensation chamber of the CO<sub>2</sub> absorber. This finding was corroborated by measuring a column of water (10-cm high) in the translucent vertical tubing connecting the condensation chamber to the inspiratory valve at the same time proximal end-expiratory airway pressure measured 10-cm H<sub>2</sub>O, and by measuring increased levels of PEEP when the volume of water in the condensation chamber exceeded an amount (approximately 200 ml) previously determined to occlude the opening of the outflow tube of the CO<sub>2</sub> absorber. The source of this water was the heated humidifier because the tubing connecting the humi-

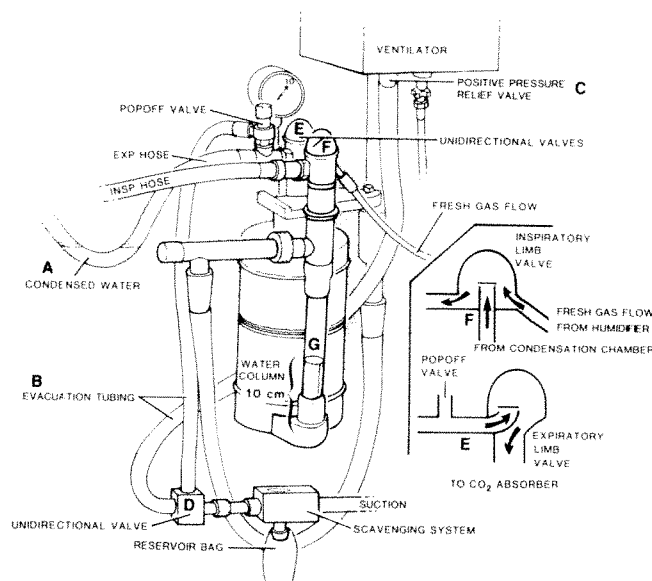


Figure 2. Illustration of a modified anesthetic circle breathing system (including mechanical ventilator and waste anesthetic gas scavenging system) showing various locations for potential increases in airway pressure.

difier to the circle anesthetic system entered just proximal to the inspiratory valve (F in Fig. 2). In this position water could be seen entering the condensation chamber intermittently during inspiration when the inspiratory valve was open, or continuously if the valve became stuck in the open position.

We have observed this complication more frequently with the routine use of heated humidifiers. This is not surprising because the rate of water condensation measured at the inspiratory valve using our humidifiers (Concha Therm, Respiratory Care Inc) set at maximum temperature (dial setting 6) and with oxygen flow rates of 5 L/min is approximately 60 ml/hr. This suggests that the complication we have reported may not be uncommon when humidifiers are used daily and the condensation chambers are not routinely drained. In addition, this complication is not unique to the Foregger CO<sub>2</sub> absorber. Indeed, we have observed PEEP result when the condensation chamber of the Ohio GMS single-canister absorber was not drained of the water of condensation from a heated humidifier.

Residual end-expiratory pressure can also result from other types of human error and equipment malfunction. An excellent review of reported causes of excessive airway pressure in the anesthetic breathing system has been written recently (2). For example, PEEP can be produced when the expiratory hose of the circle breathing system becomes obstructed with condensed water from the humidifier (A in Fig. 2).

Compression of the evacuation tubing (**B** in Fig. 2) of the scavenging system by the anesthetic machine has caused high airway pressures (3). Similarly, malfunction of the positive-pressure relief and unidirectional valves in the ventilator (**C** in Fig. 2), and in the anesthetic gas scavenging system (**D** in Fig. 2), and unidirectional valves in the circle breathing system (**E,F** in Fig. 2) have been reported to cause PEEP (4,5). Indeed, any obstruction to the flow of gas in the expiratory limb (tubing or valves) of the circle breathing system is a potential hazard for producing excessive airway pressure.

The increase in PIP resulted from the increased baseline airway pressure produced by the PEEP. The reason the magnitude of increase in PIP was less than the increase in PEEP is most likely explained by the compliance of the circle breathing system (e.g., flexible plastic hoses) and the increased lung compliance (recruitment of atelectatic alveoli) produced by the PEEP.

Low levels of PEEP (<10-cm H<sub>2</sub>O) may be beneficial in improving low arterial oxygen tension levels that can occur during surgery and general anesthesia. However, excessive PEEP in the anesthetic breathing system may produce undesirable cardiopulmonary effects. For example, high levels of PEEP (15–20-cm H<sub>2</sub>O) can decrease cardiac output (6), produce pulmonary barotrauma (6), increase extravascular lung water (7), and redistribute pulmonary blood flow (8) resulting in hypotension and systemic hypoxemia. Similarly, high PIP can produce pulmonary barotrauma (particularly pulmonary interstitial emphysema and pneumothorax) (9,10).

Several modifications of our anesthetic technique and equipment have helped in preventing recurrence of the problem. For example, changing the location of the humidified fresh gas entry site away from the inspiratory valve (e.g., along the inspiratory breath-

ing hose) prevents water from entering the condensation chamber through the inspiratory valve. Similarly, positioning the humidifier in the path of the inspiratory hose prevents water from entering the condensation chamber. Some new CO<sub>2</sub> absorbers (e.g., Ohio GMS single-canister absorber) have incorporated a window in the condensation chamber to allow early detection of accumulated water. However, the best method to avoid this complication has been increased awareness of the problem resulting in more frequent maintenance (drainage) of the CO<sub>2</sub> absorber.

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## Epidural Anesthesia for Extracorporeal Shock Wave Lithotripsy

John O. Duvall, MD, and Donald P. Griffith, MD

Extracorporeal shock wave lithotripsy (ESWL) is a new method of pulverizing urinary stones, without surgical intervention, by means of a shock wave, so that the crushed material can pass through the urinary system and out of the body. Anesthesia must be provided for two reasons: the procedure is painful, and the patient must remain still during the procedure. ESWL opens new challenges to the anesthesiologist because of the physiological effects of immersion in water, the remote monitoring required during the procedure, and the unique positioning of the patient. The following is a report of our experiences with the first 100 patients treated at The Methodist Hospital in Houston, Texas.

### Extracorporeal Shock Wave Lithotripsy

ESWL was developed in Munich, Germany, by the Dornier Aerospace Industry in conjunction with urologists at the University of Munich Grossharden Hospital over the past ten years. It employs an electrical spark to generate a shock wave underwater (Fig. 1). The amount of electrical discharge in the spark generator is 18,000–22,000 V. This shock wave is focused by an elliptical cup-like structure to a point ( $f_2$ ) above the spark. A pressure of approximately 15,000 psi is generated at the focal point ( $f_2$ ); when a crystalline object, such as a urinary stone lies in the focal point, the shock wave will shatter it into sand-like particles smaller than 2 mm, which can pass through the urinary system. The electrical spark is keyed to discharge 20 msec after the R wave of the patient's ECG, to prevent the induction of the extra-systoles seen in experimental animals during the developmental stages of ESWL.

Biological tissue has the same acoustical density and properties as water; shock waves generated in water pass through biological tissue with no change in impedance and, therefore, no tissue damage. The patient is immersed supine in a water tub filled with 37.5°C, degassed water. He is immersed from the clavicles down; the entry and exit points of the shock wave must be underwater to prevent ecchymotic skin changes. The patient is supported on a padded metal overhead frame, hydraulically operated, lying in a "lawn-chair" position while in the tub, with his arms strapped over his head (Fig. 2).

The shock wave generator is fixed to the bottom of the tub. The patient is moved to facilitate placement of the stone into the focal point of the shock wave. This aiming is accomplished by the use of two fluoroscopy units set at right angles to each other, which gives a three-dimensional picture of the stone (Fig. 3). Fluoroscopy is used to locate the stone, to aim the shock wave, and then periodically to fine-focus the shock wave impact area once the stone begins fragmenting.

### Anesthetic Considerations and Methods

Relatively speaking, one shock wave is not very painful; however it does create a bruising sensation. Anesthesia is required for the repeated waves necessary to completely fragment the stone. General or regional anesthesia can be used. Regional techniques include intrathecal and epidural. In the German experience (personal communication, Dr. C. Weber, University of Munich Grossharden Hospital, October 1983), local infiltration, sedation, or both did not prove successful in relieving the deep pain caused by the shock waves.

The main physiological considerations are the effects of immersion on the body. Studies in the aerospace medical field during zero-gravity simulations and studies of diving physiology have shown several effects. These studies, carried out with the subjects immersed in water from the neck down, showed that (1) the hydrostatic pressure of the water pressing on

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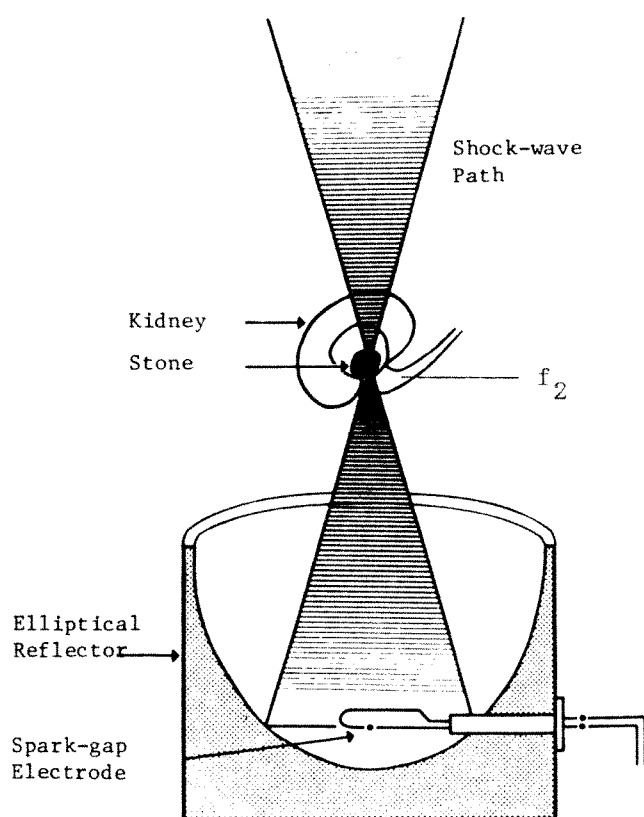


Figure 1. Diagram of shock wave generation and focusing on the stone ( $f_2$ ).

the chest and abdomen reduces the functional residual capacity of the lungs by 30–36%. Vital capacity is reduced by 22.4%. They also showed that (2) the pressure of the water squeezes the blood out of the capacitance vessels of the abdomen and the periphery, thereby increasing the central circulation volume by 700 ml. This causes a 32% increase in cardiac output, and a 35% increase in stroke volume. Pulmonary capillary blood flow increases 25–36%.

The first 100 patients in our series have all had continuous epidural anesthesia for the following reasons: 1) At first, we were not sure how long the procedures would take to completely fragment the stone. Allowances had to be made for a possible prolonged procedure. 2) At the completion of the ESWL, the patient is removed from the tub and taken to an x-ray room where a high quality abdominal film is taken to check for any remaining stone fragments that may have been missed during fluoroscopy. Should any particle larger than 2 mm remain, the patient is taken back to the lithotripsy suite, reimmersed, and re-treated. We felt that transporting a patient under general anesthesia would constitute a hazard to the pa-

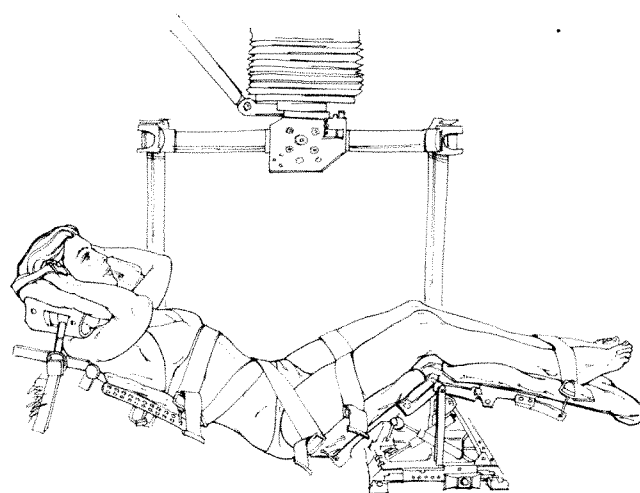


Figure 2. The patient is strapped into the support frame with the arms strapped over the head. Brachial plexus stretch injury can occur in this position.

tient. 3) Regional anesthesia also helps prevent another potential hazard—that of positioning the patient in the metal support. Because the arms are strapped in an extreme angle over the head (Fig. 2), the potential for brachial plexus stretch injury would occur. An awake patient is able to participate in his positioning in the support frame, thus avoiding harmful stretch to various parts of the body.

All patients selected for the treatments were carefully evaluated by the urologist and anesthesiologist, including ECG, intravenous pyelograms, renal tomograms, and careful medical history. All patients were ASA class I or II.

All patients were premedicated with butorphanol tartrate (Stadol) 2 mg intravenously, and atropine 0.2 mg intravenously. In all patients, the L3–4 interspace was used. The site of insertion of the epidural catheter was waterproofed with a clear, plastic, self-adhering drape. Our choice of anesthetic agent was bupivacaine (Marcaine) 0.5% initially; later on, as our techniques became more refined, and treatment times were reduced, we switched to lidocaine (Xylocaine) 2% with epinephrine. A volume of local anesthetic solution sufficient to achieve a T6 dermatomal level was injected. The patient was then taken into the lithotripsy suite, strapped into the metal support frame, and mechanically lowered into the water. After the treatment, the patient was removed from the tub and taken into an adjoining x-ray room for further radiographic evaluation.

Patient demographics and anesthetic management are summarized in Table 1.



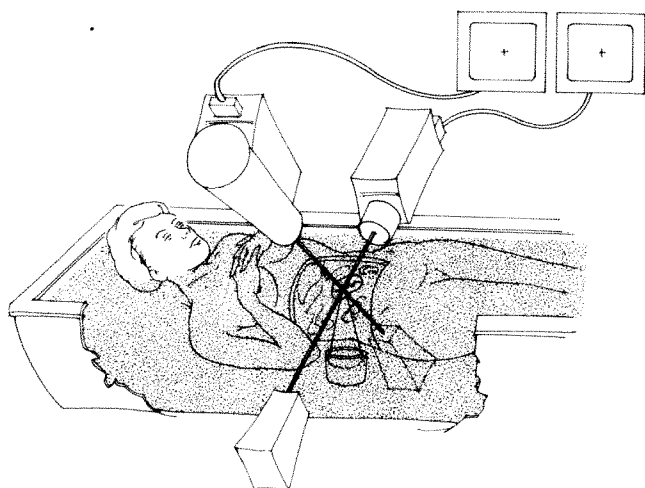


Figure 3. Fluoroscopy units are set at right angles to each other to give a three-dimensional picture of the stone and allow precision aiming of the shock wave.

## Discussion

Patient sensations have ranged from no sensation to a mild slap. Only two patients, whose blocks were marginally adequate described pain or discomfort. These patients had levels below T6; this suggests the possibility that the origin of the pain felt could be peritoneal. The majority of patients felt nothing and fell asleep during the procedure, probably as a result of a combination of the butorphanol, the warm water, and a sense of buoyancy in the water. Six patients complained of midsternal burning pain. All these patients had anesthetic levels above T6. No changes in vital signs or ECG were noted. One possibility is that this pain may originate from stimulation of the lower pleura, because in all six, the stone lay in the upper portion of the renal calyx. These patients were all relieved by intravenous butorphanol.

Relative hypotension, defined as a pressure less than 80% of preanesthetic levels, was seen in 10 patients. In 7 of these 10, immersion into the water was sufficient to restore the blood pressure to normal levels, probably because of the increased blood volume seen with immersion. The other three required vasopressors and hydration, but no patient was affected enough to cancel the procedure.

Few extrasystoles have been seen. Most of the extrasystoles were present prior to immersion, and were felt to be parasystolic beats. None of the extrasystoles presented a hazard to the patient, and they occurred infrequently.

Table 1. Patient, Procedural, and Anesthetic Data

	Average	Range
Age (yr)	46	20-73
Height (cm)	174	152-188
Weight (kg)	81	42-111
Anesthetic (ml)	28	20-35
Duration of procedure (min)	53	20-115
No. shock waves	1150	550-1600
Bupivacaine recovery time (min)	240	160-420
Lidocaine recovery time (min)	65	60-85

The switch from bupivacaine to lidocaine was made after the first 20 patients. Average ESWL time for these 20 patients was 58 min, but the recovery room time was prolonged, one patient staying 7 hr. Switching to lidocaine did not affect the intensity of the block, but significantly reduced recovery room time, thus reducing patient cost. Most patients who received lidocaine were able to move their toes upon arrival in the recovery room.

Seven patients were treated in the recovery room for nausea with promethazine. No patient required analgesics in the recovery room. Most patients complained the next day of a bruise-like soreness over the flank, which did not require parenteral analgesics.

Fifteen patients had to be removed from the water during the procedure, all for x-ray evaluation of fluoroscopically obscure stones. Time out of water was less than 30 min, and no patient required additional anesthetic solution.

We did no invasive hemodynamic monitoring, because our patient population was generally healthy. Further investigation into these areas will become necessary in higher ASA classes, as more patients present with significant cardiovascular and pulmonary disease.

In summary, ESWL is a new noninvasive method of treating urinary stones. The uniqueness of the patient environment is an anesthetic challenge, but we have found epidural anesthesia to be both safe and effective in the 100 patients we have treated.

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## Atracurium in a Patient with Pheochromocytoma

Joseph A. Stirt, MD, Raeford E. Brown JR, MD, William T. Ross JR, MD, and John S. Althaus, MS

Atracurium is a new nondepolarizing neuromuscular blocking agent of intermediate duration of action. Although most reports have noted little clinically significant change in cardiovascular variables with atracurium (1-4), alterations consistent with histamine release have been observed (5). We report, we believe, the first case in which atracurium has been used in a patient with a pheochromocytoma.

Other neuromuscular blocking drugs available at the time of this patient's operation are associated with varying degrees of histamine release, autonomic activity, and associated circulatory instability (6-10). Our own experiences in normal patients with atracurium demonstrated circulatory stability after doses providing 100% neuromuscular block (2,3). Thus we used atracurium in an attempt to provide profound neuromuscular block with minimal cardiovascular effects in a patient potentially exquisitely vulnerable to circulatory instability.

### Case Report

A 15-yr-old, 56-kg girl was admitted to the hospital the evening before surgery for elective removal of a pheochromocytoma. Fourteen months previously the patient had onset of bilateral throbbing frontal headaches lasting approximately 5 min, which gradually increased in frequency from 1 per week to 2-10 per day. The headaches were associated with profuse sweating and occasional chest palpitations. Blood pressure (BP) during these episodes reached levels up to 210/120 mm Hg.

Two months earlier, 24-hr urine analysis revealed a norepinephrine level of 1001  $\mu\text{g}/24\text{ hr}$  (normal < 80), an epinephrine level of 4.3  $\mu\text{g}/24\text{ hr}$  (normal < 25), and vanillylmandelic acid level of 31.9 mg/24 hr (normal < 8). An abdominal computerized axial tomog-

raphy scan showed a right adrenal mass 10 cm in diameter with posterior displacement of the upper pole of the kidney. A meta-iodo-benzoguanidine (MIBG) adrenal scan showed focal increased MIBG uptake in the region of the right adrenal bed. The diagnosis was pheochromocytoma.

Treatment with phenoxybenzamine and propranolol was initiated. The patient's signs and symptoms abated, and she was discharged from the hospital one month prior to the present admission on a regimen of oral phenoxybenzamine 20 mg, twice a day, and oral propranolol 40 mg, also twice a day. Elective resection of the tumor was scheduled.

On admission to the hospital on the day prior to surgery, the patient reported no headaches or diaphoretic episodes since discharge from the hospital one month earlier. Heart rate (HR) was 64 beats/min, BP was 100/80 mm Hg, and the remainder of the pre-operative physical examination and laboratory evaluation were unremarkable.

At 7 AM on the day of surgery, the patient received 5 mg of oral diazepam and 0.4 mg of oral glycopyrrolate. No sympathetic blocking agents were given. On arrival in the operating room, BP was 160/70 mm Hg and HR 68 beats/min. Fentanyl (250  $\mu\text{g}$ ) and diazepam (5 mg) were administered intravenously over the next 15 min, as a radial arterial catheter was inserted.

Induction of anesthesia with 100 mg of thiopental intravenously was followed by controlled ventilation by mask with gradually increasing concentrations of enflurane (up to 5%) in  $\text{O}_2$ . An arterial blood sample was obtained for plasma catecholamine level determinations (Table 1)(11,12). A Grass FT-10 force transducer was attached to the hand to monitor twitch tension of the thumb in response to supramaximal ulnar nerve stimulation of 0.15-msec duration at 0.15 Hz.

Atracurium (0.5 mg/kg intravenously) was administered into a rapidly running intravenous line, and 100% muscle twitch depression occurred 4 min after administration. Additional arterial blood samples for catecholamine level determinations were obtained 1 and 4 min after atracurium administration. Subse-

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Table 1. Systemic Blood Pressure, Heart Rate, and Plasma Levels of Norepinephrine (NE, pg/ml)<sup>a</sup> and Epinephrine (E, pg/ml)<sup>a</sup>

	BP (mm Hg)	HR (beats/min)	NE	E
Night before surgery	110/80	68	— <sup>b</sup>	— <sup>b</sup>
Awake, in operating room, after arterial line insertion	149/67	68	— <sup>b</sup>	— <sup>b</sup>
2 min after induction, 11 min before atracurium	155/70	55	19,896	108
11 min after induction, 2 min before atracurium	105/44	50	— <sup>b</sup>	— <sup>b</sup>
1 min after atracurium, before laryngoscopy	100/42	58	9210	75
4 min after atracurium, before laryngoscopy	97/44	60	6170	26
Post intubation, before incision				
1 min	91/43	59	6233	17
5 min	77/42	56	3970	42
15 min	72/34	50	4169	56
Post incision				
1 min	89/51	50	5532	31
5 min	82/53	52	5719	8
Peak levels during tumor manipulation	189/120	146	289,065	1514
Intraoperative, 90 min after tumor excision	82/44	108	4980	513

<sup>a</sup>Normal norepinephrine levels (supine, awake, resting) range from 50 to 300 pg/ml; normal epinephrine levels range from 0 to 60 pg/ml.<sup>b</sup>Sample not obtained.

quent samples were obtained at various times during the procedure (Table 1). Five minutes after atracurium administration, laryngoscopy was performed and 160 mg of lidocaine was sprayed into the trachea. Two minutes later, the trachea was intubated. Heart rate and blood pressure remained stable during the onset of complete neuromuscular block, and then gradually decreased over the 15 min after intubation as the inspired enflurane concentration was increased.

A central venous pressure line was inserted via the left external jugular vein. Anesthesia was maintained with 50% N<sub>2</sub>O and enflurane 3–5% in O<sub>2</sub> until the tumor had been excised. Pathologic examination later confirmed the mass to be a 96.2-gm pheochromocytoma.

After the initial 0.5 mg/kg dose of atracurium, 51 min elapsed until twitch height had recovered to 69% of the control height, at which point the first of six subsequent 0.5 mg/kg increments of atracurium was administered (surgical incision followed 18 min later). Little change in cardiovascular variables occurred after any dose of atracurium.

When surgical manipulation of the tumor began, HR and BP increased from 80 beats/min and 100/65 mm Hg, respectively, to 105 beats/min and 180/100 mm Hg. Three intravenous doses of 0.5 mg of propranolol were administered approximately 30 min apart in an attempt to control HR, with little effect; HR

increased as high as 146 beats/min after the second bolus. Sodium nitroprusside infusion at a rate of 1.25  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  was begun when BP increased, in an effort to mitigate the pressor response to tumor manipulation. The nitroprusside was then continued during the entire 2.5-hr period of tumor manipulation at a rate of 1.25–2.5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , with BP reaching a peak value of 189/120 mm Hg. In spite of the nitroprusside and propranolol, along with enflurane 3–5%, episodes of ventricular bigeminy occurred with tumor manipulation.

After the removal of the tumor, enflurane was discontinued and fentanyl was administered intravenously in increments for the duration of the procedure, which was complicated by transection of the right renal artery necessitating an end-to-side anastomosis of the renal artery to the aorta with a graft.

At the conclusion of the 7.5-hr operation, neostigmine and atropine were used intravenously to antagonize residual neuromuscular block, N<sub>2</sub>O was discontinued, the trachea was extubated with the patient awake and responsive, and she was taken to the recovery room in stable condition.

## Discussion

All of the most commonly used neuromuscular blocking agents (succinylcholine, *d*-tubocurarine, and pan-

curonium) have been employed for muscle relaxation during pheochromocytoma resection (13-15). It is difficult to determine, however, whether circulatory changes in these patients were the result of the relaxants themselves or other factors. Each of these drugs has been reported to have clinically significant cardiovascular side effects even in healthy patients without underlying cardiovascular instability (6,7).

Metocurine, advocated as an alternative relaxant with less cardiovascular activity (8,16), may release histamine (9,10), which has been associated with hypertension in patients with pheochromocytoma (17). For these reasons, and because in our own experience (2,3) and that of others (1,4) atracurium is associated with cardiovascular stability, we chose atracurium for muscle relaxation in our patient with pheochromocytoma.

Whether atracurium will ultimately prove to be the "best" relaxant for use in patients with pheochromocytoma remains to be seen. A report of the use of vecuronium, a new intermediate-duration neuromuscular blocking agent (not yet released for general use at the time of our case), in three patients with pheochromocytoma (18) showed little effect of this relaxant on heart rate or blood pressure. However, increases in plasma norepinephrine and epinephrine levels were noted after vecuronium administration, as in our case, too, at the time of tumor manipulation.

One report (5) of atracurium in normal patients documented significant decreases in blood pressure after atracurium doses of 0.6 mg/kg, and significant increases in heart rate after atracurium doses of 0.5 and 0.6 mg/kg. In that report, atracurium was administered as a 5-sec bolus, although it was not stated whether the drug was injected into a distant peripheral port in an intravenous line or directly into a vein. Recently, clinical evidence of histamine release was reported to follow atracurium administration directly into the venous system (19).

Our own experience (2,3) and a more recent report (4), in which atracurium was administered into a rapidly flowing intravenous line and thus diluted somewhat, showed no clinical evidence of histamine release or cardiovascular side effects after atracurium. Perhaps, as has been suggested (19), the technique of injection is related to the subsequent presence or absence of histamine release, circulatory effects, or both. If so, prudence suggests injection of atracurium into a rapidly flowing peripheral intravenous line.

Studies of the histamine-releasing properties of vecuronium and atracurium indicate that both have less potential for histamine release than metocurine (9,10), a relaxant considered by some to be the neuromuscular relaxant with the least effect on the cardiovas-

cular system (20). Should this information be confirmed by future clinical experience, atracurium and vecuronium would seem to be the relaxants of choice for patients undergoing pheochromocytoma resection.

That the potential for cardiovascular instability existed in the patient we described above is borne out by the increases in heart rate and blood pressure seen with manipulation of the tumor despite high (3-5%) concentrations of enflurane along with sodium nitroprusside and propranolol. Blood pressure and heart rate remained stable during the onset of 100% neuromuscular block in the 4 min immediately after atracurium administration, but gradually decreased over the subsequent 15 min (Table 1) as the inspired enflurane concentration was increased.

Plasma catecholamine levels, elevated above normal immediately after anesthesia induction, appeared to parallel changes in arterial blood pressure throughout the case (Table 1). Thus the lower catecholamine levels seen after atracurium probably reflect increasing depth of enflurane anesthesia during the time period surrounding atracurium administration (e.g., the arterial blood pressure) rather than any catecholamine-lowering effect of atracurium.

The relative stability of plasma catecholamine values after atracurium (Table 1), when subsequent tumor manipulation produced marked increases, suggests that atracurium had little effect on catecholamine secretion in this patient, in whom the potential for large-scale release was present.

In summary, atracurium was used to produce muscle relaxation in a patient with pheochromocytoma. Cardiovascular stability and little change in catecholamine levels accompanied the onset of 100% neuromuscular block after atracurium. Further study of the effects of atracurium in patients with pheochromocytoma appears warranted.

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## Treatment of Severe Bronchial Asthma with a Low-Pressure Chamber and 100% O<sub>2</sub>

Karl Lenggenhager, MD

Despite modern hospital treatment, there are still patients who die during asthmatic attacks (1-4). The high-altitude climate encountered in the Engadin in Switzerland (1740 m) is well known to have a beneficial effect on asthmatic patients (5). To some extent this could be due to the reduced atmospheric pressure, because Tromp and Bouma in 1974 (6) obtained encouraging results with patients during asthmatic attacks when using a simulated altitude of between 2000 and 2500 m. We describe the successful treatment of two severely asthmatic patients at a simulated altitude of 7000 m with 100% O<sub>2</sub>. We further demonstrate, by means of two physical models, that the resistance of a narrow passage to the flow of air decreases as barometric pressure is reduced.

### Case Reports

A 25-yr-old male medical student suffered from bronchial asthma severe enough to produce cyanosis with respiratory wheezing. These symptoms completely disappeared in our low-pressure chamber when 100% O<sub>2</sub> was given at a simulated altitude of 5500 m. Pressure was further reduced to a simulated altitude of 7000 m for 30 min, and the patient felt well. Upon returning to atmospheric pressure, cyanosis and wheezing reappeared within 10 min.

A 50-yr-old woman developed a severe asthmatic attack immediately after cholecystectomy. This was her third attack; she was unconscious and deeply cyanotic. No low-pressure chamber was available and with artificial respiration and administration of 100% O<sub>2</sub> it took about an hour for her condition to improve. In the course of a subsequent attack, she was placed in a low-pressure chamber. Her wheezing and cyanosis disappeared as soon as a simulated altitude of 5500 m had been reached in 100% O<sub>2</sub>.

### Model Experiments

Two models are described. In the first model the volume of gas flowing into the model was maintained constant; whereas in the second, the pressure within the model was held constant.

In Figure 1 two identical fingercots (1 and 2) were rhythmically inflated by a balloon pump (3) delivering a constant volume of air at a frequency of 2 strokes/sec. The air escaped from the system through a narrow tube (4). A screw applied to the inlet of fingercot 2 was tightened to the point at which the fingercot became progressively inflated.

With the same setting of the screw, the model was brought to a simulated height of 3500 m. Fingercot 2 now emptied between the strokes of the pump, suggesting that a stenosis of the same geometry offers a lower resistance to the outflow of gas when the barometric pressure is reduced. By further tightening the micro-screw at 3500 m, fingercot 2 again could be made to undergo progressive filling. As shown in Table 1, further reduction of barometric pressure allowed for emptying of fingercot 2 through an increasingly severe stenosis in 5500 and 7000 m.

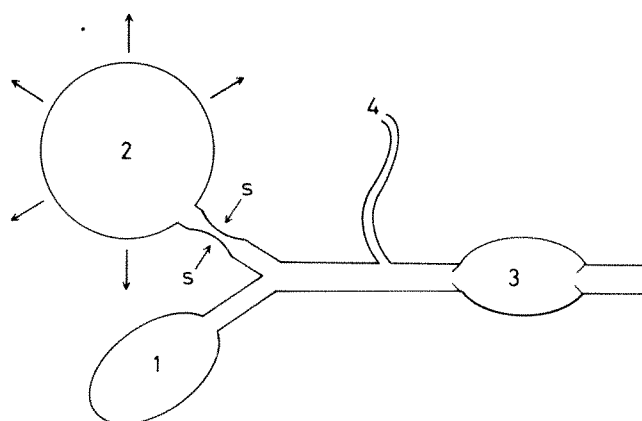
A detailed description of the second model (Fig. 2) has been given (7). The pumping rate needed to maintain a pressure of 90 mm Hg above barometric pressure within this system with a fixed stenosis in the outflow pathway was measured at increasing simulated heights. Average values of six trials are listed in Table 2. In steady state (90 mm Hg above atmospheric pressure) the volume added to the system per unit time must be equal to the volume lost through the outlet. Thus with increasing simulated altitude, the volume escaping through the fixed area of stenosis per unit time increased.

### Discussion

The model experiments indicate that the resistance across a given stenosis decreased as the ambient pressure is reduced. This principle also applies to respiratory exchange, although the relationship between

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**Figure 1.** Model of airways. Two identical rubber fingercots (1,2) communicate through glass and rubber tubes. The system is filled by a pump (3) and empties through a narrow tube (4). A variable stenosis is inserted between fingercot 2 and the outlet. For results, see text and Table 1.

**Table 1.** Diminishing Effect of Stenosis at Increasing Simulated Altitudes

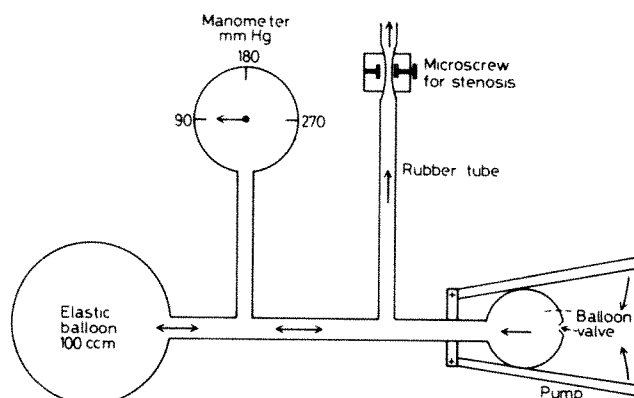
Degree of stenosis (relative units)	Valley	3500 m	5500 m	7000 m
18	—	—	—	—
20	+	—	—	—
22	+	+	—	—
24	+	+	+	—

—, No dilation of fingercot 2 (Fig. 1).

+, Progressive dilation of fingercot 2 (Fig. 1).

volume flow and ambient pressure is not linear (8,9). Flow within the airways of the human lungs is partly laminar, partly turbulent (9). Resistance to laminar flow (pressure gradient divided by volume flow) is independent of gas density and flow velocity; resistance to turbulent flow, however, is proportional to gas density (mass per unit volume) as well as to velocity (8,9). When breathing a given volume of tidal air through narrowed airways, as is the case in bronchial asthma, the gas has to flow at higher velocities and the flow will tend to change from laminar to turbulent. Lowering gas density, on the other hand, results in partial replacement of turbulent flow by laminar flow (9).

Mechanics of respiration at altitude are complicated by the fact that less difference of pressure can be generated by the same muscle force when the ambient pressure is reduced (10). This adverse effect of high altitude is obviously more than compensated for by the effect of low air density, which leads to a reduction in the resistance of the airways. Maximal breathing capacity in normal subjects is reported to increase 36% when ambient pressure is reduced to one-third of an atmosphere (11).



**Figure 2.** Diagram of a model with a fixed stenosis in the outflow tube. Filling pressure is held at 90 mm Hg above ambient pressure, and the simulated altitude is varied. For results, see text and Table 2.

**Table 2.** Pumping Rate<sup>a</sup> Necessary to Maintain a Pressure Head of 90 mm Hg

Meters above sea level	Barometric pressure (mm Hg)	Pump strokes (per min)
500	712	60
3500	493	92
5000	405	112
6000	354	148

Note that with decreasing ambient pressure, the rate of flow increases.  
<sup>a</sup>See Figure 2.

In conclusion, the clinical observation that the resistance of airways is reduced at high altitudes is supported by model experiments, by theoretical considerations, and by measurements of the maximal breathing capacity. The use of low barometric pressure in combination with 100% O<sub>2</sub> represents an additional means for treatment of severe asthma. Further studies using low-pressure chambers first in aviation medical centers and later in hospitals are indicated to provide quantitation of the therapeutic benefit achieved by decreasing ambient pressure in the management of severe asthma. Unconscious asthmatics should be fixed in a sitting position with their legs horizontal in order to facilitate greater expansion of the lungs.

I wish to thank Dr. M.L. Pressler, Dr. J.A.S. McGuigan, and especially Dr. S. Weidmann (head of the Physiological Institute, Bern University Medical School) for their help with the manuscript.

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## Sinus Arrest Associated with Cimetidine

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Cardiac dysrhythmias including infrequently observed episodes of asystole are associated with the use of cimetidine (1-8). The following case of a critically ill patient who was scheduled for emergency transthoracic pacemaker insertion because of two episodes of asystole emphasizes the need to appreciate these side-effects.

### Case Report

A 20-yr-old man was admitted to our emergency room after being involved in an automobile accident. Physical examination revealed multiple trauma that included a left hemopneumothorax, a fractured left clavicle, a blunt abdominal injury, and a pale, pulseless left hand. After initial stabilization, the patient was taken to the operating room where a lacerated spleen was removed. An intraoperative angiogram demonstrated a normal thoracic aorta with occlusion of the proximal left subclavian artery. Postoperatively, the patient's hemodynamic status slowly stabilized, but a persistent bronchopleural fistula necessitated a return to the operating room where a large laceration of the left upper lobe and complete avulsion of the bronchus, artery, and vein of the left lower lobe superior segment were found. A left upper lobectomy and superior segmentectomy were performed. Soon thereafter, the patient developed deep venous thrombosis of the left lower extremity, and a heparin infusion was started. Subsequently, the development of facial edema and cyanosis suggested a superior vena caval thrombosis. Inability to achieve adequate heparinization prompted a hematologic workup which revealed an antithrombin III deficiency. Replacement of this factor facilitated therapeutic anticoagulation.

On the ninth hospital day, the patient had two episodes of prolonged sinus arrest. The first of these

resolved without intervention in about 15 sec; however, the second episode, 6 hr later, resolved only after a precordial thump was applied. The patient was scheduled for emergency insertion of a transthoracic pacemaker; a transvenous approach was deemed inappropriate because of the suspected superior vena caval thrombosis. At the time of these episodes, the patient was receiving cimetidine, digitalis for prophylaxis against postlobectomy atrial dysrhythmias, and oral antacids. Laboratory data revealed a sodium level of 131 mEq/L, potassium of 5.2 mEq/L, and calcium of 8.2 mg/dl. Serum digitalis level was subtherapeutic, and an electrocardiogram showed sinus tachycardia with T-wave inversion in the inferior leads.

During the preanesthetic evaluation, we noted that the patient had been receiving 300 mg of intravenous cimetidine as a 10-15 min constant infusion every 6 hr for several days as prophylaxis against gastric bleeding secondary to stress ulceration. On further investigation, it became apparent that both episodes of asystole occurred within 5 min of starting infusions of cimetidine. Therefore, after developing contingency plans to start an isoproterenol infusion and perform immediate pacemaker insertion should sinus arrest occur, we discontinued the drug and postponed surgery. The patient was observed closely over the next 24 hr during which no further episodes of asystole occurred. He has since been discharged from the hospital and has experienced no further difficulty with his cardiac rate or rhythm.

### Discussion

Cimetidine is currently approved by the US Food and Drug Administration for the prophylaxis and short-term treatment of duodenal ulcers and for palliation of gastric hypersecretory disorders (9). Its advent into the realm of the anesthesiologist came with the use of cimetidine as a premedicant to decrease gastric volume and increase gastric pH prior to the induction of general anesthesia (10,11). The anesthesiologist also encounters the drug frequently in the intensive care setting where it is used for the prevention of gastric bleeding secondary to physiologic stress, although it

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is still not clear whether cimetidine offers any advantage over oral antacids (12).

Sinus bradycardia, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation have been reported after the use of intravenous and, in the case of bradycardia, oral cimetidine (1-7). Rare episodes of fatal and nonfatal sinus arrest have also been described (3,8). Although a definite relationship has not been established, these dysrhythmias have shown a consistent temporal association with the use of cimetidine and have resolved with discontinuance of the drug. Typically, the dysrhythmias have been observed after several doses. In addition, the dysrhythmia has consistently recurred when the patient was rechallenged with cimetidine (1,2,6).

In our patient, the fact that both episodes of asystole were related temporally to the administration of cimetidine and that no further episodes occurred after discontinuing the drug suggests that cimetidine was the cause of the dysrhythmia. Digoxin was initially considered a contributing factor; however, the serum digitalis level was shown to be subtherapeutic, and evidence suggests that histamine receptor blockade with cimetidine attenuates histamine-augmented digitalis and ouabain cardiotoxicity (13).

Histamine is present in relatively high concentrations in cardiac tissue (14) where it exerts a positive inotropic and chronotropic effect and a negative dromotropic effect (15-18). This property appears to be expressed by specific myocardial histamine receptors rather than by indirect stimulation of cardiac  $\beta$ -receptors because cimetidine attenuates these effects, whereas  $\beta$ -blockade does not (16). The negative dromotropic effect of histamine, demonstrated in one study as prolongation of the PR interval, was antagonized in a dose-dependent fashion by blockade of  $H_1$  but not  $H_2$  receptors (18). The positive chronotropic and inotropic effects seem to be  $H_2$  phenomena, whereas the negative dromotropic effect and a coronary spasm effect are mediated by the  $H_1$  receptor (15-19). It is proposed that  $H_2$  receptors exist in the SA node and in the myocardium of the atria and ventricles while  $H_1$  receptors appear to be present in the AV node and coronary vessels (18).

The mechanism by which cimetidine causes abnormalities of cardiac rate and rhythm is still not entirely clear. The answer may involve the amount of histamine stimulation present at the time the cimetidine is given, and the interplay of the  $H_1$  and  $H_2$  receptors. For instance, in our patient,  $H_2$ -receptor blockade during a period of histamine stimulation may have negated the chronotropic effects of histamine on the heart while allowing predominance of the  $H_1$ -mediated negative dromotropic effect. Therefore, si-

nus arrest with the concurrent development of AV dissociation could be produced. This interesting role of histamine seems to become important only in times of maximum cardiac stress and apparently serves as an extreme compensatory mechanism. Such appears to have been the case in our patient as well as in the majority of patients described in the literature.

In addition to the cardiac effects, cimetidine is associated with other problems that are pertinent to the anesthesiologist. Precipitous hypotension has been described with the use of the drug (20). The  $H_2$  receptor is involved in the mediation of bronchodilation, and cimetidine may actually decrease the threshold for bronchospasm in a susceptible patient (21). Primarily by decreasing hepatic blood flow and inhibiting drug-metabolizing enzymes in the liver, cimetidine can interfere with the metabolism of many drugs including propranolol and diazepam, thereby potentiating their effects (22,23). This has been demonstrated clinically in the coronary care unit where patients with therapeutic serum levels of lidocaine have been shown to develop toxic levels after introduction of cimetidine (24). It would seem logical, as suggested by Melmon and Nierenberg (23), that any drug dependent upon hepatic metabolism for elimination may have a prolonged half-life when used during cimetidine administration.

In summary, this case reemphasizes that there is a risk of dangerous dysrhythmias occurring with the use of cimetidine. A knowledge of such an association prevented the occurrence of a major operation in the critically ill patient described.

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## Letters to the Editor

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### Violent Fasciculations May Not Signal Pseudocholinesterase Deficiency

To the Editor:

We read with interest the recent report by Glasser (1) on violent fasciculations in a patient found to have pseudocholinesterase deficiency. Glasser suggests that this occurrence may be a useful observation in detecting this deficiency.

Glasser cites work by Baraka (2) to show that patients with normal pseudocholinesterase will not have violent fasciculations after 10 mg of succinylcholine. Other authors, using the "self-taming" technique of injecting 10 mg of succinylcholine before a subsequent larger dose report different results. Brodsky et al. (3) and Siler et al. (4) reported "3+" (maximum) fasciculations after 10 mg of succinylcholine in 10 and 4% of their normal patients, respectively. I have used this self-taming technique personally on several hundred patients, and I estimate violent fasciculations to have occurred in 5% of those receiving an initial 10-mg dose.

Lee-Son et al. (5) and Azar and Betcher (6) report the use of minute doses of succinylcholine in patients known to have pseudocholinesterase deficiency. The doses given to produce twitch depression of 90% were on the order of 7 mg. No mention of fasciculations, violent or otherwise, was made. I have used the same technique on a patient with pseudocholinesterase deficiency, also noting no fasciculations.

I conclude that violent fasciculations may occur in normal patients approximately 5% of the time when 10 mg of succinylcholine is administered. Although only a small number of cases is reported, it would appear that no fasciculations may occur when giving a smaller dose to patients with pseudocholinesterase deficiency. I therefore question both the sensitivity and specificity of this method as a means of detecting pseudocholinesterase deficiency.

Instead, I advocate the method proposed by Savarese (7) whereby 0.1 mg/kg of succinylcholine is administered to a patient after anesthesia is induced. A duration of apnea of greater than 5 min should be cause for withholding further succinylcholine.

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#### In Response:

Dr. Sosis attributes a conclusion to my article (1) that I did not make and proceeds to question it. He also did not take into account the method of administration of low-dose succinylcholine in his arguments.

Baraka's work (2) on "self-taming" doses of succinylcholine was cited to illustrate the low incidence of violent fasciculations after 10 mg of succinylcholine. Indeed, none of his 40 patients had violent fasciculations. Although Brodsky et al. (3) did show a 10% incidence of "+3" fasciculations after a 10-mg dose of succinylcholine, Siler et al. (4) showed a 4% incidence of "+3" fasciculations after the subsequent 1 mg/kg intubating dose. These investigations and presumably Dr. Sosis's own data used an intravenous bolus injection.

Low-dose infusion rates of succinylcholine are less likely to produce fasciculations than a bolus injection (5), and the patient in my case report received 10 mg of succinylcholine over a 1-min period.

Although Lee-Son et al. (6) and Azar and Betcher (7) did not refer to fasciculations when administering low-dose succinylcholine to their patients with known atypical pseudocholinesterase, an initial 2-mg succinylcholine bolus in Azar and Betcher's patient caused an "increase in the twitch response, probably due to repetitive firing." Perhaps with a larger dose, this repetitive firing may have resulted in visible fasciculations.

The method of Savarese (8) cited and used by Dr. Sosis would render a patient with atypical pseudocholinesterase apneic for 30-60 min. Although this test may be preferable to screening all patients preoperatively for dibucaine number and pseudocholinesterase level (this was the reason for



Dr. Savarese's letter) this would not be suitable for a short procedure such as that performed on my patient (a D & C).

I do not take issue with Dr. Sosis regarding the sensitivity or specificity of my observation, because this was not the intent or the conclusion presented in the report. This is a clinical caveat in a situation that is likely to occur in practice: the use of low-dose succinylcholine infusion during short general anesthetics. Should violent fasciculations occur, stop the infusion and think of the diagnosis of atypical pseudocholinesterase.

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## Use of Intravenous Glucose Solutions in Surgical Patients

To the Editor:

A recent article by Fassoulaki et al. (1) describes the occurrence of hepatic centrilobular injury in fasted rats, pretreated with phenobarbital to induce enzyme activity, when exposed to 6% oxygen for 15, 30, or 42 min. A second group of rats were not deprived of food, were pretreated with phenobarbital, and were exposed to 6% oxygen for 46 min. The authors state that the group of "fed rats had less hepatic injury ( $5.7 \pm 3.0\%$ ) than did rats deprived of food and breathed 6% oxygen for 42 min ( $38.4 \pm 3.8\%$ ). They conclude that "these data appear to support the soundness of infusing glucose before and during anesthesia and surgery." This recommendation may not be appropriate for all patients, even patients with hypoxia.

As a neuroanesthesiologist, the organ of my chief concern is the brain, which is quite vulnerable to ischemic injury that might occur during neurovascular procedures such as carotid endarterectomy, extracranial vascular anastomosis, or aneurysm clipping. Several studies on cerebral ischemia (a pathologic decrease in cerebral blood flow) have

demonstrated that fed rats exposed to complete or incomplete ischemia sustain massive cerebral injury manifested by disruption of the cerebral metabolites (2); that cats and monkeys exposed to incomplete ischemia have less neurologic functional recovery than animals exposed to complete ischemia (3); that fasted rats given 2 ml of 50% glucose solution prior to ischemia develop a severe intracellular lactic acidosis with marked disruption of the cerebral energy state compared to fasted animals that develop only mild lactic acidosis and maintain the normal energy state (4); that cats treated with 6 g of glucose prior to cerebral ischemia have greater accumulation of brain lactic acid and marked disruption of the cerebral energy state than do fasted cats (5); and that food-deprived monkeys tolerate 14 min of circulatory arrest with minimal neurologic and histopathologic changes, whereas monkeys given 5% glucose in saline prior to arrest remain decerebrate and opisthotonic with widespread necrosis of the cortex and basal ganglia (6).

Uncomplicated hypoxia is a reduction in oxygen delivery with unlimited supply of substrate. This results in an increase in cerebral blood flow. Continued supply of glucose in the presence of hypoxia results in the accumulation of lactic acid (7). Thus both hypoxia and ischemia result in progressive lactic acidosis that may become excessive. Excessive tissue acidosis may induce cellular edema and hasten the development of cell damage (8).

Whereas circulatory arrest or complete global cerebral ischemia are more severe insults than our patients sustain, many do experience incomplete cerebral ischemia or complete focal ischemia during the neurosurgical procedures. Because of this, our department and several other anesthesia departments avoid glucose-containing solutions in neurosurgical patients. Because glucose may benefit some organs while being detrimental to others, the liver, the brain, and other organs must be considered when choosing the appropriate intravenous solutions for our surgical patients.

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## Saline with Benzyl Alcohol Prevents Pain of Needle Insertion: True But Dangerous

To the Editor:

Thomas (1) is correct that, when raising skin wheals prior to placing intravenous catheter needles, physiological saline with 0.9% benzyl alcohol is less painful than lidocaine or any other local anesthetic solution. But, the principal use of this solution as stated on the label is "to dilute and dissolve drugs" (see Fig. 1).

If regional anesthesia is administered in the same area (operating theatre, induction room, etc.) where intravenous fluids are started, having physiological saline with 0.9% benzyl alcohol available may be dangerous. Diluting local anesthetic solutions with it has resulted in myelopathy (2).

To conclude, a "brief burning and stinging" from lidocaine (1) or another local anesthetic solution when raising a skin wheal is preferable to neuropathy or myelopathy.

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Figure 1. Solution to which Thomas (1) refers.

## Significant Differences

To the Editor:

I would like to comment on the recent discussion of "statistically significant vs clinically significant differences" (*Anesth Analg* 1984;63:1050). Statistical tests are usually used to quantify the chance that an observed difference is due to sampling or random error, when in fact no real difference exists between the groups being compared. A  $P$  value of less than 0.05 has become the sole criterion for deciding whether or not a difference is "statistically significant."

The universal application of this criterion has important implications. If the odds at arriving at a falsely positive conclusion are 1 in 19 ( $P = 0.053$ ), the hypothesis is rejected, and the observed difference is attributed to random error. If the odds are reduced only to 1 in 21 ( $P = 0.048$ ), the hypothesis is accepted. Clearly the universal application of a cut-off  $P$  value of 0.05 is unwarranted.

When the  $P$  value is close to 0.05, another approach could be taken. The article could include the number of subjects tested, the observed difference between groups, the statistical test used, and the exact  $P$  value obtained from that test. Readers could then decide for themselves whether or not the observed difference was "statistically significant," and, if so, whether or not the difference is "clinically significant."

This compromise should satisfy Dr. Berman, and Dr. Mirakhur and colleagues.

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## Electric Shock Injuries in Hospitals

To the Editor:

In association with Doctor Paul Leonard of the Mayo Clinic, I am preparing a review on the use of electricity in hospitals.

At one time it was bruited that as many as 5000 patients per year were electrocuted by medical instruments or hospital wiring. Over a 25-yr period, however, the actual number of reasonably documented electric shock incidents appears to be about three dozen, of which very few were fatal.

We would appreciate hearing from anyone who has knowledge of authenticatable instances of patient injury due to electricity that have not been reported previously in the open literature. Information and inquiries may be addressed to me at Box 617, Groton, Massachusetts 01450.

John M. R. Bruner, MD

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## Book Reviews

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### Clinical Anesthesia in Neurosurgery

Elizabeth A.M. Frost, ed. Boston: Butterworth Publishers, 1984, 480 pp, \$49.95.

Neuroanesthesia has grown in complexity concomitant with the extensive development of the neurosciences and neurosurgery. *Clinical Anesthesia in Neurosurgery*, edited by Elizabeth A.M. Frost is a laudable endeavor to address the unique problems of anesthetic management in neurosurgery. The collaborative effort of 15 anesthesiologists and neurosurgeons stresses a team approach to neurosupportive care.

The initial chapters present cerebral physiology, its alterations due to disease and anesthetics, and the means of evaluating it clinically. Noteworthy is an authoritative and practical chapter on electrophysiologic monitoring. The following chapters present the management of neurosurgical disease entities ranging from cerebral vascular diseases, tumors, pediatric entities, spine disorders, and peripheral nerve injury to debilitating seizures and cancer pain states requiring ablative procedures.

The section on management of head and spinal cord injury is usually comprehensive in scope. The final chapters provide a brief overview of postanesthetic care, the criteria and the controversies for brain deaths associated with the right to die, and "no code" situations.

The writing style is relatively consistent and clear, in part due to the major participation of the editor as an author in 9 of the 21 chapters. The text is replete with references, tabulated easy-to-read details, illustrations, and photographs of clinical significance. Inclusion of historical highlights of experimental studies rounds out the text. In general, clinical chapters are quite self-contained with minimal repetition elsewhere in the text—a convenience for easy consultation.

This book fulfills a need for an up-to-date reference on neuroanesthesia. It complements rather than replaces the existing texts. It will be an excellent resource for anesthesiologists and neurosurgeons in training and in practice. Intensivists and emergency physicians will also find much information on neurosupportive care.

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### Manual of Cardiac Anesthesia

Stephen J. Thomas, MD, ed. New York: Churchill Livingstone, 1984, 469 pp, \$27.50.

This book aims at the first time or infrequent practitioner of cardiac anesthesia. As such, it stresses those facts, concepts, and caveats that might appropriately receive first priority when initially encountering this subdiscipline. It is not a comprehensive text and does not seek or claim to be. But neither is it a cookbook limiting itself to a dogmatic approach without supplying any rationale for its suggested practices.

As a multiauthored text it reads smoothly in spite of its outline format without an undue amount of repetition. Its contents include the basics of the most common cardiac problems seen by the anesthesiologist, their pathophysiological features with salient points of management, and the pertinent aspects of cardiopulmonary bypass. The approach is informative without being rigid, the style is informal without being breezy, and the emphasis is on the pragmatic rather than the esoteric. Whether evaluating the patient preoperatively, discussing ramifications for anesthetic management of a specific clinical or technical problem, or conveying concepts of pharmacology or coagulation, the commonplace and the practical are stressed.

The novice cardiac anesthesiologist will find this book useful if not comprehensive. Brevity in the text, however, can be supplemented by chapter bibliographies including recent entries that are frequently subcategorized by clinical problem or drug.

Prejudice against this manual focuses on the limited or absent treatment of certain less common clinical problems or drugs. Bias for the book is that it does a good job of assigning and communicating those topics of first importance in cardiac anesthesia.

This manual along with its bibliographical entities would serve the short-term newcomer to the cardiac operating room well. Perhaps a greater value would be in the role of an adjunct text. Overlooking the price, the book meets its goals for its intended audience. It is so recommended as a useful and worthy purchase.

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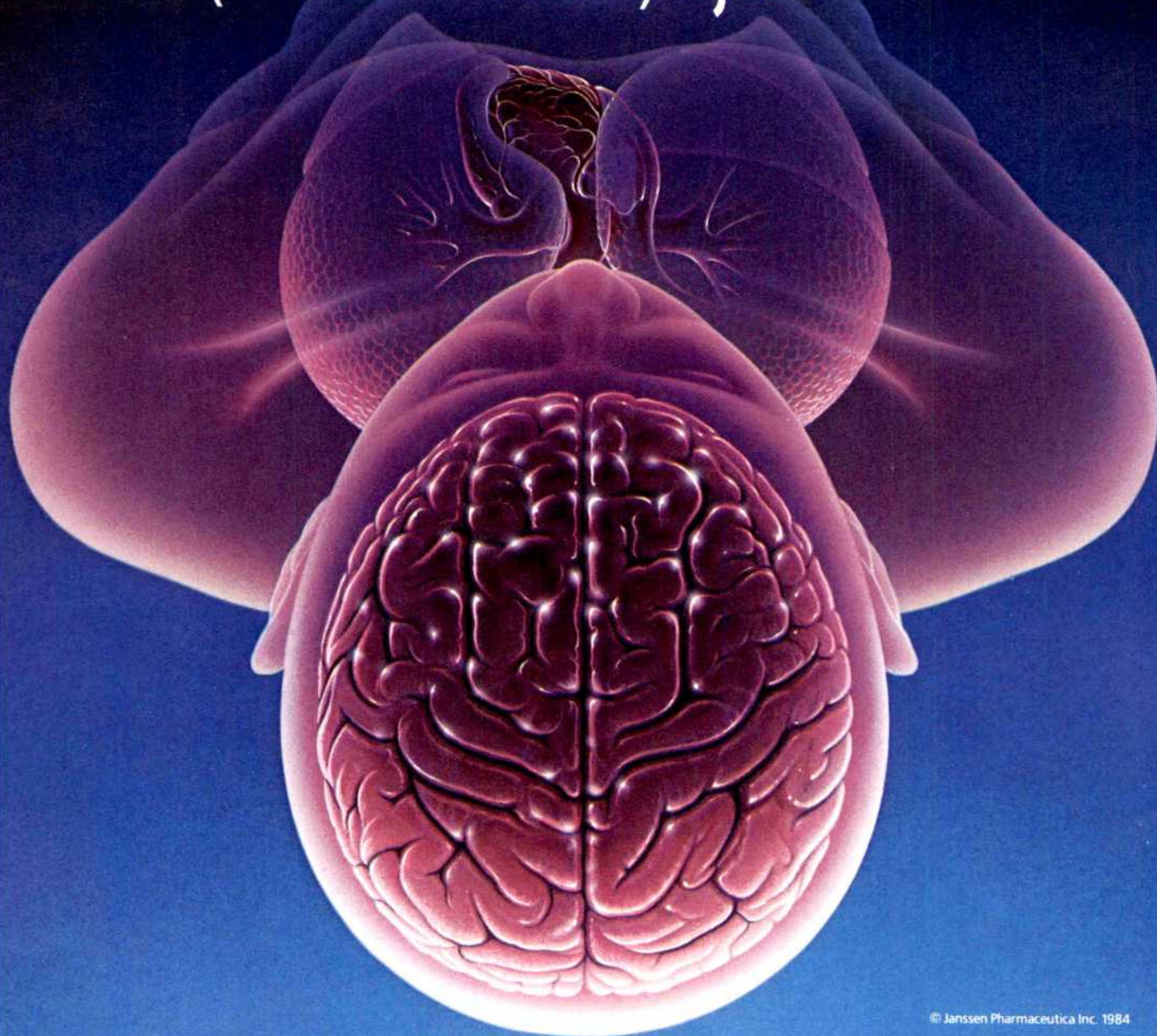


# ANESTHESIA RECORD

SUMMARY OF PRE OPERATIVE FINDINGS    SEX *F*    RACE    AGE *40*    WEIGHT *52.5 kg*    HABITUS    TEETH *upper & partial lower denture*  
BP *128/90*    TPR *37/80/*    HGB HCT *12.7 / 37.6*    URINALYSIS *1.09*    OTHER LAB DATA    FOOD INTAKE *NPO*  
p *45.0*  
It *ketones*  
PHYSICAL STATUS *II*    PRE OPER. DIAGNOSIS *Malignant Melanoma*    PRE OP. VITAL *Yes*

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- Superior hemodynamic stability
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1. Scientific Exhibit, Sufentanil vs. Isoflurane in Major Orthopedic Procedures (Fahmy NR, Principal Investigator), March 1983.

2. Fahmy NR, Beemer GH, Roberts JT. Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

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3. Smith NT, Dec-Silver H, Harrison WK, et al: ASA Abstract, Anesthesiology (Suppl) 57: A291, 1982.

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# SUFENTA®

## (sufentanil citrate) Injection

**CAUTION:** Federal Law Prohibits Dispensing Without Prescription

### DESCRIPTION

SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-phenylethyl)-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-7.5.

### CLINICAL PHARMACOLOGY

SUFENTA is an opioid analgesic. SUFENTA is approximately 5 to 7 times as potent as fentanyl. (Dosage requirements for equianalgesic effect will be 1/5-1/7 those of fentanyl on a mg/kg basis.) At doses of up to 8 µg/kg, SUFENTA provides profound analgesia; at doses  $\geq$  8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 0.72 minutes, redistribution of 13.7 minutes and an elimination half-life of 148 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl; at dosages of  $>2.6$  µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of  $\geq 8$  µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at dosages of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of fentanyl.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

### INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated:

as an analgesic adjunct at dosages of up to 8 µg/kg in the maintenance of balanced general anesthesia; as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position; to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

### CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

### WARNINGS

**SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.**

**An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.**

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence can be reduced by: 1) administration of up to 1/3 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg; 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion; or 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

### PRECAUTIONS

The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Drug Interactions: An additive effect with SUFENTA may be exhibited in patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

**Pregnancy Category C:** SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

**Animal Toxicology:** The intravenous LD<sub>50</sub> of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

### ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia

Gastrointestinal: nausea, vomiting

Respiratory: apnea, postoperative respiratory depression, bronchospasm

Dermatological: itching

Central Nervous System: chills

Miscellaneous: intraoperative muscle movement

### DRUG ABUSE AND DEPENDENCE

SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

### OVERDOSAGE

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD<sub>50</sub> of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD<sub>50</sub>s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

### DOSAGE AND ADMINISTRATION

The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses  $\geq$  8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

**Usage in Children:** For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg/kg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

**Premedication:** The selection of preanesthetic medications should be based upon the needs of the individual patient.

**Neuromuscular Blocking Agents:** The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART		
TOTAL DOSAGE	MAINTENANCE DOSAGE	
1-2 µg/kg: administered with nitrous oxide-oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	10-25 µg (0.2-0.5 ml): as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.	
2-8 µg/kg: administered with nitrous oxide-oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli; provide hemodynamic stability and provide relatively rapid recovery.	25-50 µg (0.5-1 ml): as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.	
8-30 µg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages $\geq$ 8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	25-50 µg (0.5-1 ml): as determined by changes in vital signs that indicate stress and lightening of anesthesia.	

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

### HOW SUPPLIED

SUFENTA (sufentanil citrate) injection for intravenous use is available as:

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# Soothing news for busy anesthesiologists

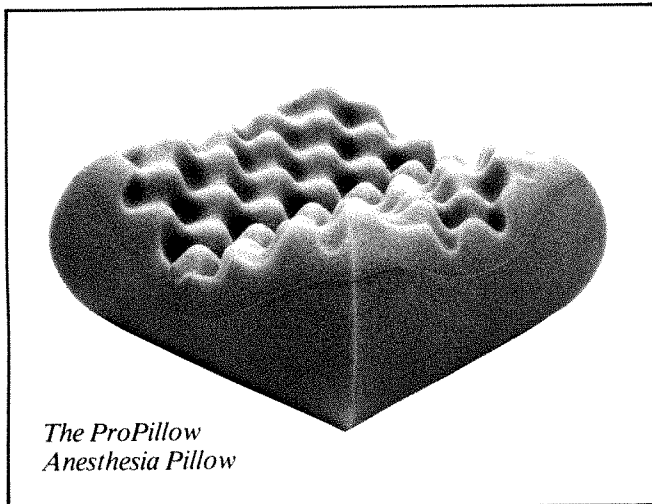
Dr. Smith was having another busy day in surgery. One Swan-Ganz placement had been unusually time-consuming. Plus the patient had been difficult to intubate. To top it off, the pump time had been excessive.

Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

But these two stories don't end here. About 28 days later, *both patients had a bald spot about the size of a silver dollar at the occiput. . . exactly where their heads were resting on the table for hours on end.* They were each advised by their surgeons that they had a 50% chance of their hair growing back within the next year. But there was an equal chance that their hair wouldn't grow back at all. The anesthesiologists on both cases were never told of the problem.

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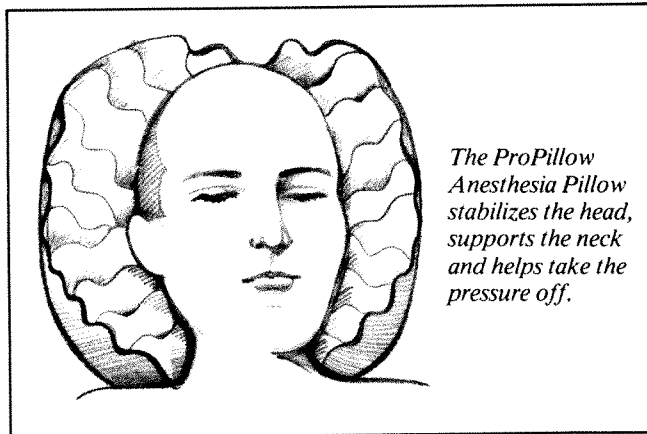
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**ETHRANE® (enflurane)** is an inhaled anesthetic. The MAC (minimum alveolar concentration) in middle-aged humans is 1.68% in oxygen and 0.57% in 70% nitrous oxide. The blood/gas partition coefficient is 1.91 at 37°C.

Enflurane obtunds pharyngeal and laryngeal reflexes. Changes in the inspired concentration of enflurane can rapidly change anesthetic depth. Enflurane depresses ventilation, and deeper levels of anesthesia can produce high PaCO<sub>2</sub> levels with spontaneous ventilation.

Blood pressure and cardiac output decrease with induction of anesthesia. Surgical stimulation tends to restore these variables to near normal levels. Increases in depth of anesthesia decrease pressure and output. Heart rate and ventricular rhythm are little affected by enflurane. Enflurane may slightly sensitize the heart to the arrhythmogenic effects of epinephrine.

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Analgesic concentrations of enflurane (0.25% to 1%) do not significantly depress the rate or force of uterine contraction, and normally do not appreciably affect uterine blood loss or Apgar scores. Concentrations of 1% to 2% depress the rate and force of uterine contraction, and 2% to 3% may abolish contractions. Concentrations of 1.5% to 3% diminish or abolish the uterine response to oxytocin. Concentrations exceeding 1% for vaginal delivery or cesarean section may increase uterine bleeding. In patients given

1% enflurane in 70% nitrous oxide for therapeutic termination of pregnancy, mean estimated blood loss is 40 ml—versus 20 ml in patients given only a local anesthetic. The peak levels of serum fluoride after enflurane anesthesia in humans (average 15 µM/l) are well below the 50 µM/l threshold for minimal renal damage in normal patients. However, patients taking isoniazid or other hydrazine-containing compounds may metabolize more enflurane, and peak serum fluoride levels can exceed 50 µM/l.

#### **CONTRAINDICATIONS**

Seizure disorders (see WARNINGS).

Known sensitivity to **ETHRANE® (enflurane)** or other halogenated anesthetics. Known or suspected genetic susceptibility to malignant hyperthermia.

#### **WARNINGS**

Convulsive activity may be associated with the use of enflurane, particularly with deep anesthesia (greater than 3% enflurane) and/or with hypocapnia.

Only vaporizers producing predictable concentrations of enflurane should be used. Hypotension and respiratory depression can serve as indicators of deeper levels of anesthesia. Greater circulatory depression may result from enflurane administration in patients who are hypovolemic or who have myocardial dysfunction.

If unexplained hepatic dysfunction followed a previous exposure to a halogenated anesthetic, consideration should be given to use of an agent other than enflurane.

#### **PRECAUTIONS**

**General:** **ETHRANE® (enflurane)** should be used cautiously in patients with a medical or drug history suggesting a greater susceptibility to cortical stimulation.

**Information for Patients:** As with other anesthetics, enflurane may slightly decrease intellectual function for two to three days after anesthesia. Similarly, small changes in

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and a predictable recovery of neuromuscular function.

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**Pregnancy Category B:** Reproduction studies in rats and rabbits given four times the human dose of enflurane revealed no impairment of fertility or harm to the fetus. However, no adequate studies have been done in pregnant women, and enflurane should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Enflurane may be excreted in human milk and caution should be exercised when enflurane is administered to a nursing mother.

**Malignant Hyperthermia:** In susceptible individuals, enflurane may trigger a hypermetabolic state and the clinical syndrome of malignant hyperthermia. The syndrome includes muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure (these nonspecific signs also may appear with light anesthesia, acute hypoxia, etc.). The increase in metabolism may elevate temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and increase the usage of the CO<sub>2</sub> absorption system (hot canister). PaO<sub>2</sub> and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support, and management of electrolyte-fluid-acid-base derangement. Renal failure may appear and urine flow should be sustained if possible.

#### ADVERSE REACTIONS

1. Malignant hyperthermia (see PRECAUTIONS). 2. Deep levels of enflurane anesthesia and/or light levels with hypocapnia may produce convulsive activity. 3. Hypotension and respiratory depression may occur. 4. Arrhythmias, shivering, nausea, and vomiting have been reported. 5. Leukocytosis has been observed. 6. Unexplained mild, moderate, and severe liver injury may rarely follow anesthesia with enflurane.

#### OVERDOSAGE

To treat overdosage, stop drug administration, establish a clear airway, and assist or control ventilation with pure oxygen.

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**Matthew Hussey, Ph.D.**, Head, Department of Physics,  
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Physicians using diagnostic ultrasound, radiographers, and medical or nursing students will find that **Basic Physics and Technology of Medical Diagnostic Ultrasound** is essential reading for a better understanding of the role of ultrasound in medicine.

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- 3 Generating and Detecting Ultrasound
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- 6 Static B-Mode Instruments
- 7 Dynamic (Real-Time) B-Mode Scanning
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- 11 Safety of Diagnostic Ultrasound

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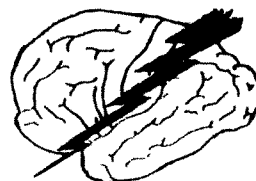
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### PAVULON®

(pancuronium bromide, injection)

### BRIEF SUMMARY

(Please consult package insert for full prescribing information.)

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS

**ACTIONS:** Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

**CONTRAINDICATIONS:** Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

**WARNINGS:** PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

**USAGE IN PREGNANCY:** The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

**PRECAUTIONS:** Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

**ADVERSE REACTIONS:** Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

**DRUG INTERACTION:** The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

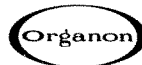
Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

**DOSAGE AND ADMINISTRATION:** Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

**CAUTION:** Federal law prohibits dispensing without prescription.

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Please see preceding page for brief summary of prescribing information.



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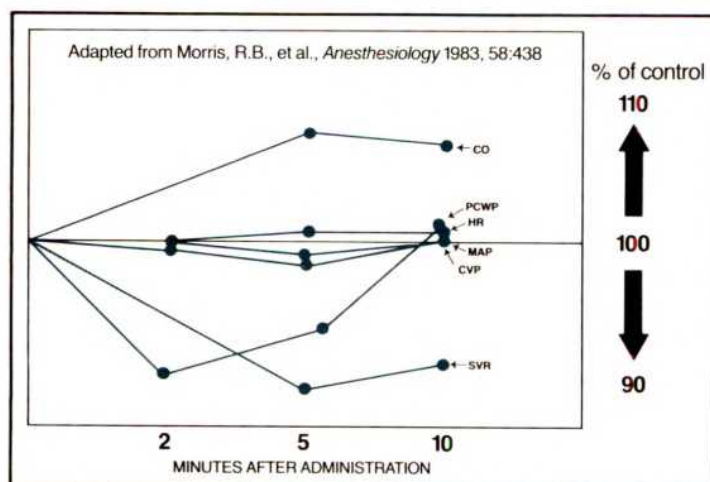
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# In neuromuscular blockade...

# Closest to the ideal:



## Free of clinically significant cardiovascular effects

NORCURON is the only surgical muscle relaxant for which no clinically significant adverse cardiovascular effects have been observed in clinical trials.<sup>1-3</sup> This makes NORCURON unique among all neuromuscular blocking agents in clinical use.<sup>4</sup>

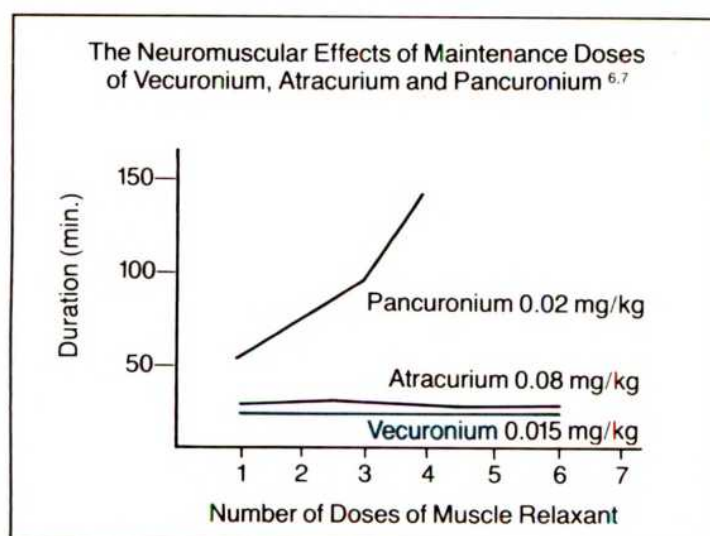
The Effect of Non-depolarizing Muscle Relaxants on Histamine Levels, Mean Arterial Pressure and Heart Rate<sup>5</sup>

Drug	Dose (mg/kg)	xED <sub>95</sub>	Percent of Control		
			Histamine	Mean Arterial Pressure	Heart Rate
tubocurarine	0.5	1	318	78	116
metocurine	0.5	2	212	79	119
atracurium	0.6	3	192	80	108
vecuronium	0.1	1.7	117	100	99
vecuronium	0.2	3.5	87	99	102

## Histamine release unlikely to occur

Histamine release has not been observed with NORCURON...as shown by preliminary clinical experience. In doses up to 3.5 times the ED<sub>95</sub>, it causes no increase in circulating histamine nor does it decrease systemic blood pressure.<sup>5</sup>

Hypotension and tachycardia tend to occur when histamine levels are increased to about 200% of control.<sup>5</sup>



## No clinically significant cumulative effects seen

With NORCURON cumulative effects are not seen in clinical practice. The interval between repeated doses has been found to remain constant between as many as six to ten repeated administrations.<sup>6,7</sup>



# NORCURON<sup>®</sup>

(vecuronium bromide for injection)

## Safety Index and Comparative Safety Ratios<sup>8</sup>

$$\text{Safety Index} = \frac{\text{ED}_{50} \text{ autonomic inhibition}}{\text{ED}_{95} \text{ neuromuscular blockade}}$$

### Comparative Safety Ratios

#### For Vagolytic Effects

gallamine	1:1
pancuronium	3:1
atracurium	25-30:1
vecuronium	60:1

#### For CV/Histamine Related Effects

d-tubocurarine	1:1
metocurine	2:1
atracurium	3:1
vecuronium	*

\*cannot be calculated since it does not cause any CV or histamine related effects

## Outstanding safety profile

The Safety Index helps quantify the improved safety of the newer muscle relaxants on a relative basis. The characteristics of cardiovascular effects and histamine release are areas where the new agents, particularly NORCURON, have made the most significant gains.<sup>8</sup>

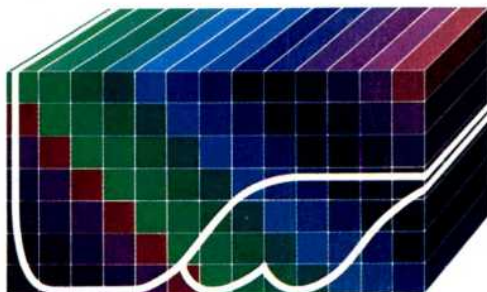
The Safety Index is described as the  $\text{ED}_{50}$  for autonomic inhibition over the  $\text{ED}_{95}$  for neuromuscular blockade.<sup>8</sup>

## A Comparison of Surgical Muscle Relaxants vs. The Ideal<sup>4</sup>

("+" signifies proximity to the ideal)

Characteristic	Vecuronium	Atracurium	Pancuronium	Succinylcholine	D-tubocurarine
Onset of Action	-	-	-	+	-
Histamine Release	+	-	+	+	-
Cardiovascular Side Effects	+	+/-	-	-	-
Duration of Action	+	+	-	+	-
Cumulative Effects	+	+	-	-	-
Rate of Recovery	+	+	-	+	-
Reversibility	+	+	+	-	+
Potency	+	+	+	-	-
Non-depolarizing	+	+	+	-	+
Metabolite Activity	+	+	+	+	+

\*Currently under evaluation.



## NORCURON<sup>®</sup>

(vecuronium bromide for injection)

### Closest to the ideal

Of the newer short- to intermediate-acting drugs, NORCURON has the most ideal profile, specifically attributable to its outstanding safety features relating to cardiovascular side effects and histamine-releasing properties.<sup>4</sup>





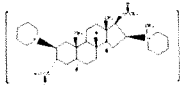
1. Durant NN. Norcuron® — A new non-depolarizing neuromuscular blocking agent. *Semin Anesth* 1:47-56, 1982. 2. Morris RB, Cahalan MK, Miller RD, et al: Cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 58:438-440, 1983. 3. Krieger N, Cruik JF, Booy LH: Relative potency of ORG NC45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 52:783-787, 1980. 4. Miller RD (ed): *Innovations in Surgical Muscle Relaxants*. Far Hills, NJ, Gardiner-Caldwell Synmed, 1984. 5. Basta SA, Savarese JJ: Comparative histamine-releasing properties of vecuronium, atracurium, tubocurarine and metocurine, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC45, vecuronium bromide)*. Amsterdam, Excerpta Medica, 1983. p. 183. 6. Foldes FF, et al: Muscular relaxation with atracurium, vecuronium and Duodur under balanced anaesthesia. *Br J Anaesth* 55 (suppl. 1): 97S, 1983. 7. Fahey MR, Morris RB, Miller RD, et al: Clinical pharmacology of ORG NC45 (Norcuron®): a new non-depolarizing muscle relaxant. *Anesthesiology* 55:6, 1981. 8. Clinical Courier, Vol. 2, No. 4, July 1984.

## NORCURON® (NC-45)

Vecuronium Bromide for Injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

**DESCRIPTION:** NORCURON® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2*β*, 3*α*, 5*α*, 16*β*)-17*β*-bis (acetyl-oxy)-2-(1-piperidinyl) androst-16-yl]-1-methyl-, bromide. The structural formula is



Norcuron® is supplied as a sterile freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

**CLINICAL PHARMACOLOGY:** Norcuron® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equivalent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED<sub>50</sub> (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2 to 3 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® (vecuronium bromide for injection) may be decreased by approximately 15% (see Dosage and Administration Section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to a 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started the neuromuscular block produced by Norcuron® (vecuronium bromide for injection) is readily reversed with various anticholinesterase agents, e.g., pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

**Pharmacokinetics:** At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg, systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of the injected dose. 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron® (vecuronium bromide for injection); equivalent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half of the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from the patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary-capillary-wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease.) Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® (vecuronium bromide for injection) has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

**INDICATIONS AND USAGE:** Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** None known.

**WARNINGS:** NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

**PRECAUTIONS:**

**Renal Failure:** Norcuron® (vecuronium bromide for injection) is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

**Altered Circulation Time:** Conditions associated with slower circulation time in cardiovascular disease, old age, or edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

**Hepatic Disease:** Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in recovery from Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

**UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.**

**Severe Obesity or Neuromuscular Disease:** Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron® (vecuronium bromide for injection).

**Malignant Hyperthermia:** Many drugs used in anesthetic practice are suspected of being capable of triggering potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

**Drug Interactions:** Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY).

The use of Norcuron® (vecuronium bromide for injection) before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied. Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

**Inhalational Anesthetics:** Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

**Antibiotics:** Parenteral intrapleural administration of high doses of certain antibiotics may intensify or produce a neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® (vecuronium bromide for injection) during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

**Other:** Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

**Drug-laboratory test interactions:** None known.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

**Pregnancy; Pregnancy Category C:** Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

**Pediatric Use:** Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 11/2 times as long to recover. Information presently available does not permit recommendations for usage in neonates.

**ADVERSE REACTIONS:** Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

**OVERDOSAGE:** There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Norcuron® (vecuronium bromide for injection) can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve. Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine) may be used to reverse the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

**DOSAGE AND ADMINISTRATION:** Norcuron® (vecuronium bromide for injection) is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS: Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain the maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1/4 to 1/5 times the ED<sub>50</sub>) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® (vecuronium bromide for injection) is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended, after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. If less frequent administration is desired, higher maintenance doses may be administered.

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

**Dosage in children:** Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 11/2 times as long to recover. See also sub-section PRECAUTIONS titled Pediatric use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

**COMPATIBILITY:** Norcuron® is compatible in solution with

0.9% NaCl solution	5% glucose in saline
5% glucose in water	Lactated Ringers

**HOW SUPPLIED:** 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 12. NDC 0052-0442-10.

**STORAGE:** PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

**AFTER RECONSTITUTION:** Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.

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Journal of the International Anesthesia Research Society

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NARCAN (0.4 mg/ml) is available in 1-ml ampuls and 10-ml vials. Also available, NARCAN<sup>®</sup> NEONATAL INJECTION (naloxone hydrochloride). Each 2-ml ampul contains 0.02 mg/ml.

For brief summary of prescribing information, see next page.  
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Narcotic Antagonist

Brief Summary of Prescribing Information

**INDICATIONS AND USAGE** NARCAN is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic narcotics, propoxyphene, methadone and the narcotic-antagonist analgesics: nalbuphine, pentazocine and butorphanol. NARCAN is also indicated for the diagnosis of suspected acute opioid overdosage.

**CONTRAINDICATIONS** NARCAN is contraindicated in patients known to be hypersensitive to it. **WARNINGS** NARCAN should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN.

NARCAN is not effective against respiratory depression due to non-opioid drugs. **PRECAUTIONS** In addition to NARCAN, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been reported. These have occurred in postoperative patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with pre-existing cardiac disease or patients who have received potentially cardiotoxic drugs.

**Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity and mutagenicity studies have not been performed with NARCAN. Reproductive studies in mice and rats demonstrated no impairment of fertility.

**Use in Pregnancy:** Pregnancy Category B. Reproduction studies performed in mice and rats at doses up to 1,000 times the human dose, revealed no evidence of impaired fertility or harm to the fetus due to NARCAN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NARCAN should be used during pregnancy only if clearly needed.

**Nursing Mothers:** It is not known whether NARCAN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NARCAN is administered to a nursing woman.

**ADVERSE REACTIONS** Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, larger than necessary dosage of NARCAN may result in significant reversal of analgesia, and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with the use of NARCAN postoperatively (see PRECAUTIONS & USAGE IN ADULTS—POSTOPERATIVE NARCOTIC DEPRESSION). Seizures have been reported to occur infrequently after the administration of naloxone, however, a causal relationship has not been established.

**OVERDOSAGE** There is no clinical experience with NARCAN overdosage in humans.

In the mouse and rat the intravenous LD<sub>50</sub> is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD<sub>50</sub> (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injection; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

**DOSAGE AND ADMINISTRATION** NARCAN may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN the patient should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary.

**Intravenous infusion** NARCAN may be diluted for intravenous infusion in normal saline or 5% dextrose solutions. The addition of 2 mg of NARCAN in 500 ml of either solution provides a concentration of 0.004 mg/ml. Mixtures should be used within 24 hours. After 24 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient's response.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. NARCAN should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to NARCAN unless its effect on the chemical and physical stability of the solution has first been established.

**USAGE IN ADULTS Narcotic Overdose—Known or Suspected** An initial dose of 0.4 mg to 2 mg of NARCAN may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of NARCAN have been administered, the diagnosis of narcotic induced or partial narcotic induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

**Postoperative Narcotic Depression** For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN are usually sufficient. The dose of NARCAN should be titrated according to the patient's response. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal, i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of NARCAN may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or circulatory stress.

Repeat doses of NARCAN may be required within one or two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

**USAGE IN CHILDREN Narcotic Overdose—Known or Suspected** The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, NARCAN may be administered I.M. or S.C. in divided doses. If necessary, NARCAN can be diluted with sterile water for injection.

**Postoperative Narcotic Depression** Follow the recommendations and cautions under Adult Postoperative Depression. For the initial reversal of respiratory depression NARCAN should be injected in increments of 0.005 mg to 0.01 mg intravenously at two to three minute intervals to the desired degree of reversal.

**USAGE IN NEONATES Narcotic-Induced Depression** The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M., or S.C. This dose may be repeated in accordance with adult administration guidelines for postoperative narcotic depression.

**HOW SUPPLIED**—NARCAN (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration is available as:

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6108-6/Rev Nov 1984

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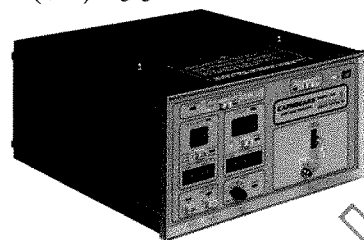
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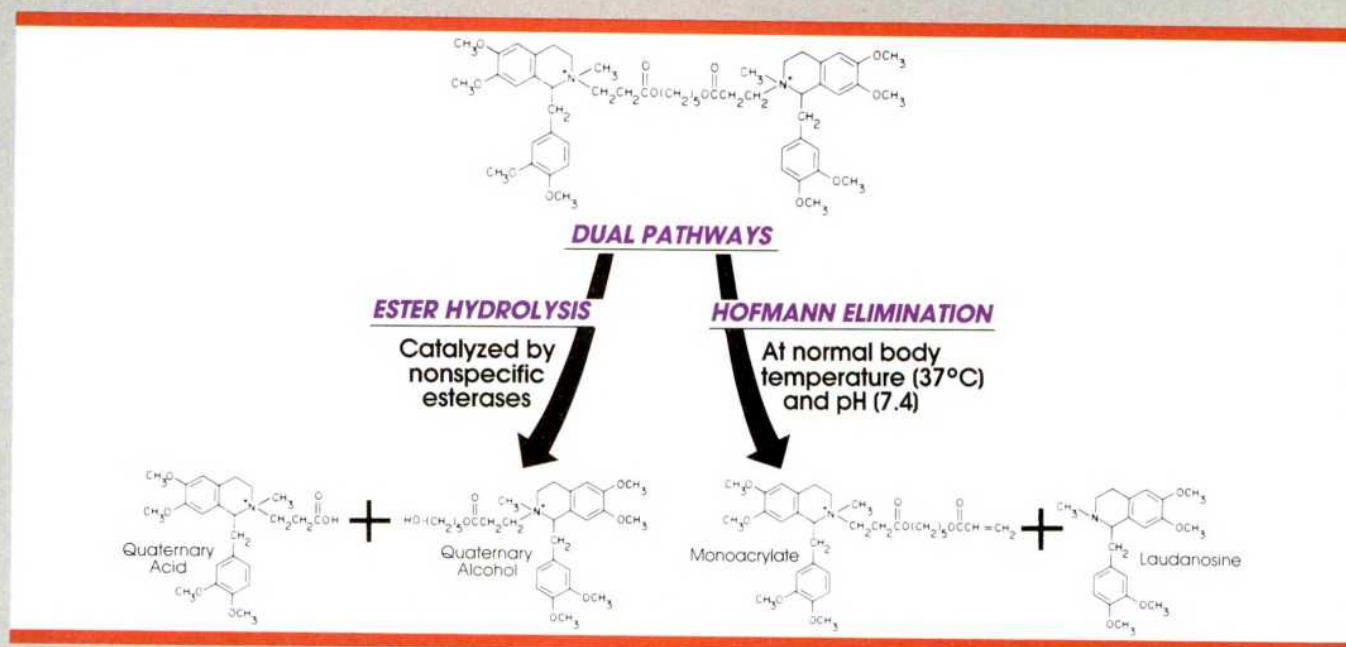
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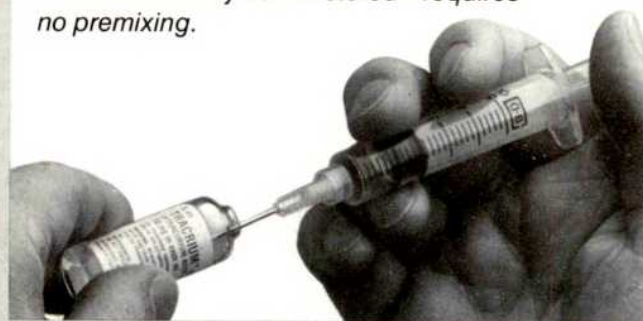
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*"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."*<sup>1</sup>

*"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."*<sup>2</sup>

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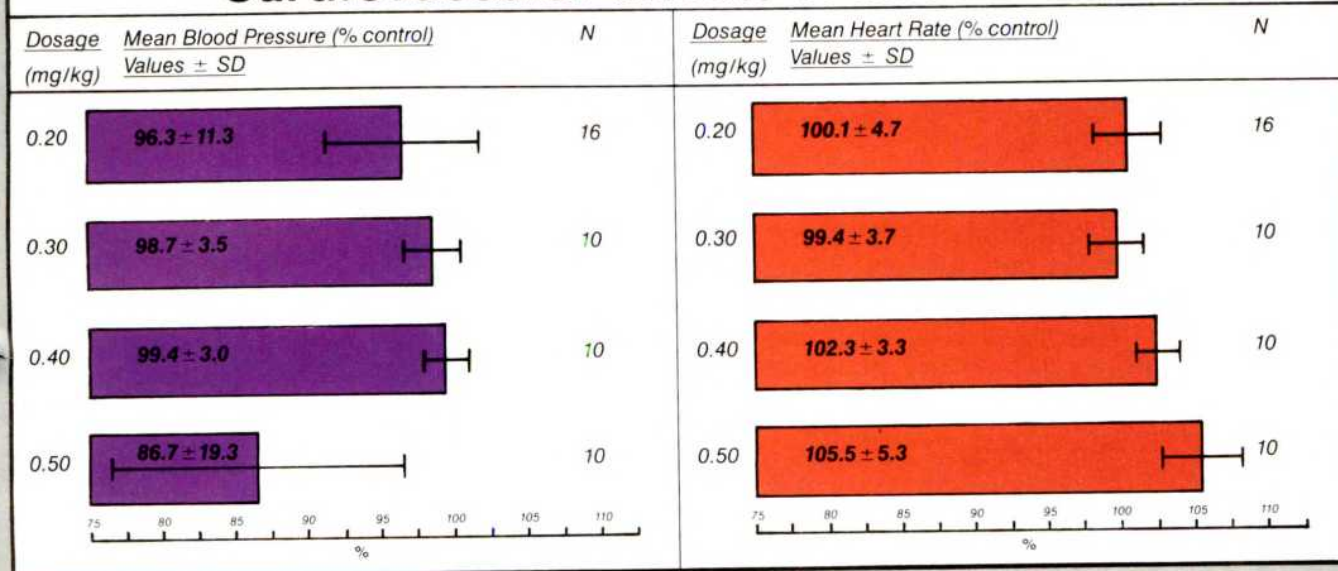




## Few Cardiovascular Effects at Recommended Dosages

□ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.

### Cardiovascular effects of atracurium



Adapted from Basta et al.<sup>3</sup>

## No Cumulative Effects Upon Recovery, After Multiple Doses

□ Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time

□ Once recovery begins, it is relatively rapid and independent of dose

□ This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."<sup>1</sup>

## Minimal Histamine Release

□ Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine

□ Clinically significant histamine release occurs well within the clinical dosage range (at ED<sub>95</sub>) for curare, at the upper limits of the clinical dosage range (at 2  $\times$  ED<sub>95</sub>) for metocurine and outside the clinical dosage range (at 3  $\times$  ED<sub>95</sub>) for atracurium<sup>4</sup>

□ The lack of hemodynamic changes due to Tracrium suggests minimal histamine release

Please see brief summary of prescribing information on the following page.

#### REFERENCES:

1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. *Seminars in Anesthesia* 1982; 1:57-62.
2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. *Anesth Analg* 1982; 61:730-734.
3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. *Anesth Analg* 1982; 61:723-729.
4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. *Anesthesiology* 1982;57:A261.

**TRACRIUM® INJECTION**  
(atracurium besylate)



## TRACRIUM® INJECTION (atracurium besylate)

**DESCRIPTION:** Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

**INDICATIONS AND USAGE:** Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it.

**WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebation. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

### PRECAUTIONS:

**General:** Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered, however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** The neuromuscular blocking action of Tracrium may be enhanced by enflurane, isoflurane, halothane, certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Pregnancy: Teratogenic Effects:** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been

administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 2 years have not been established.

**ADVERSE REACTIONS:** Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

In the United Kingdom, where Tracrium has been marketed since December, 1982, the most frequent adverse reactions reported in association with the use of Tracrium are cutaneous histamine-like reactions, bronchospasm, and bradycardia. These have been reported to occur in about one in 10,000 patients. Less frequent adverse reactions are hypotension, heart arrest, tachycardia, cyanosis, and apnea, which have been reported to occur in approximately one in 100,000 patients.

**DOSAGE AND ADMINISTRATION:** Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

**HOW SUPPLIED:** Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10). Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4179507

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**TRACRIUM® INJECTION**  
(atracurium besylate)

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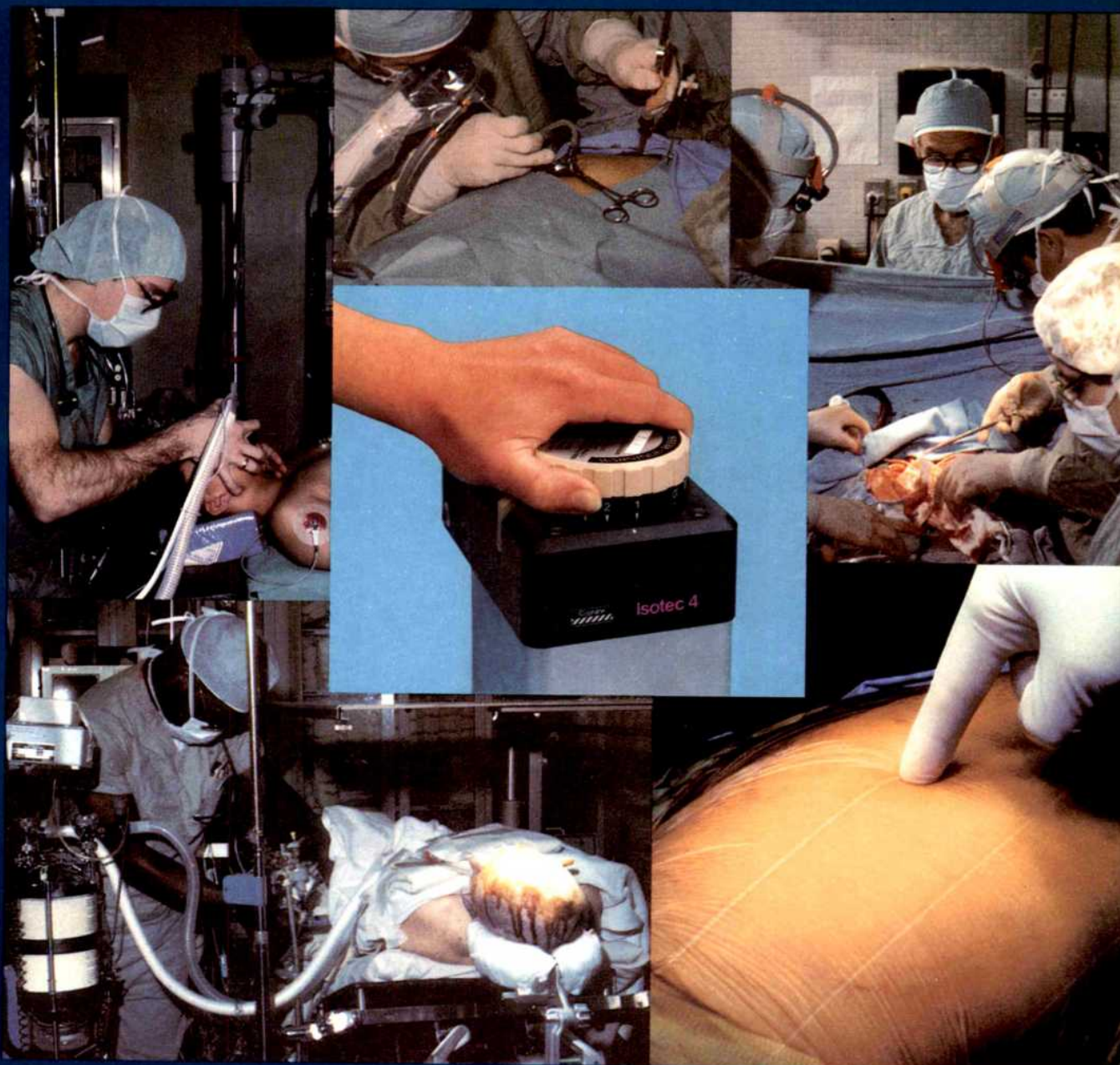
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# **Forane<sup>®</sup> (isoflurane)**

## **The Versatile Anesthetic**



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**Forane<sup>®</sup> (isoflurane)**

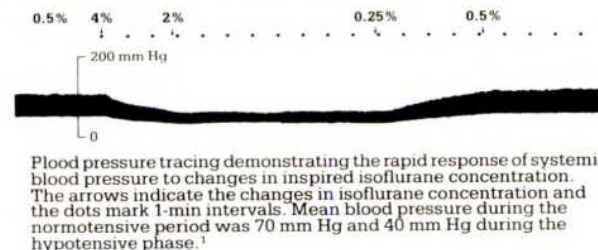




# Forane<sup>®</sup> (isoflurane) The Versatile Anesthetic

## A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.<sup>1</sup>



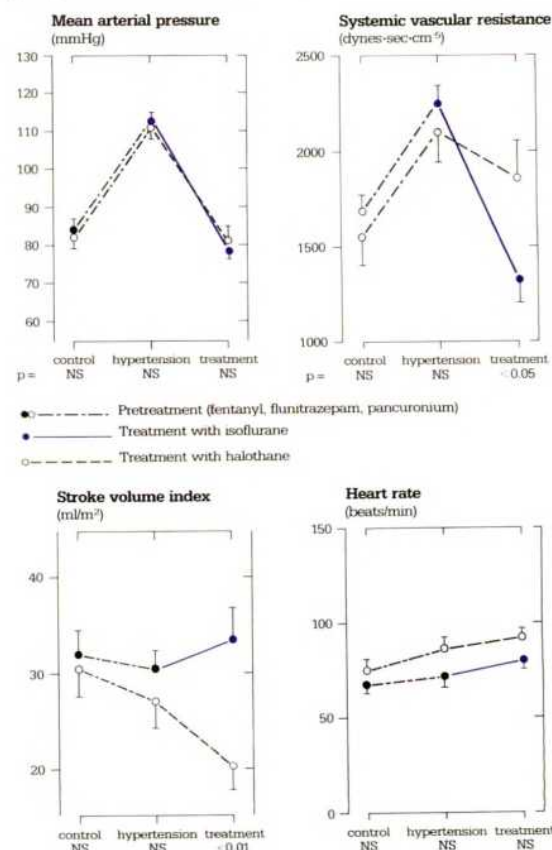
## Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when  $\text{PaCO}_2$  is controlled at 25-30 torr, and ICP may be readily lowered during surgery by decreasing  $\text{PaCO}_2$ .<sup>2</sup>

## Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery. (Adapted from Hess et al<sup>3</sup>).



## Potential of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).<sup>4,5</sup> Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

## Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."<sup>6</sup>

## A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."<sup>7</sup> (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.<sup>8</sup>

Post-laparoscopy Nausea (N) and Vomiting (V)		
Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N <sub>2</sub> O, O <sub>2</sub>	37	23 (62%)*
isoflurane, fentanyl, O <sub>2</sub>	20	6 (30%)
isoflurane, O <sub>2</sub>	20	5 (25%)

Adapted from Alexander et al<sup>8</sup> \*p<0.05

### References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. *Anesth Analg* 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. *Anesthesiology* 54:97-99, 1981.
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5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709.
6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? *Anesth Analg* 60(9):666-682, 1981.
7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981.
8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. *Anesth Analg* 63:175, 1984.

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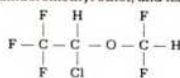
**Forane® ...a product of original Anaquest research**  
(isoflurane)



# Forane® ... The Versatile Anesthetic (isoflurane)

**CAUTION:** Federal Law Prohibits Dispensing without Prescription

**DESCRIPTION:** FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Some physical constants are:

Molecular weight	184.5
Boiling point 760 mm Hg	48.5°C (Uncorr)
Refractive index $n_D^{20}$	1.2990—1.3005
Specific gravity 25°C/25°C	1.496
Vapor pressure in mm Hg **	
	20°C 238
	25°C 295
	30°C 367
	35°C 450

\*\* Equation for vapor pressure calculation:

$$\log_{10} P_{\text{vap}} = A + \frac{B}{T} \quad \text{where: } A = 8.056 \quad B = -1664.58$$

$$T = ^\circ\text{C} + 273.15 \text{ (Kelvin)}$$

Partition coefficients @ 37°C	
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8
Partition coefficients @ 25°C—rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinylchloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec and 23°C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec and 23°C	Greater than useful concentration in anesthesia

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

**CLINICAL PHARMACOLOGY:** FORANE (isoflurane) is an inhalation anaesthetic. The M.A.C. (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N <sub>2</sub> O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation of tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. **RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY.** As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO<sub>2</sub>, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 ml of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE. THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

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**INDICATIONS AND USAGE:** FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

**CONTRAINDICATIONS:** Known sensitivity to FORANE (isoflurane) or other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

**WARNINGS:** Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients

undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

**PRECAUTIONS: General:** As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

**Information to Patients:** Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

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**Malignant Hyperthermia:** In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO<sub>2</sub> absorption system (hot canister). PaO<sub>2</sub> and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

**ADVERSE REACTIONS:** Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting, and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

**OVERDOSAGE:** In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

**DOSAGE AND ADMINISTRATION: Premedication:** Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

**Inspired Concentration:** The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

- vaporizers calibrated specifically for isoflurane;
- vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula

$$\% \text{ isoflurane} = \frac{100 P_A F_V}{F_T (P_A - P_V)}$$

where  $P_A$  = Pressure of atmosphere  
 $P_V$  = Vapor pressure of isoflurane  
 $F_V$  = Flow of gas through vaporizer (ml)  
 $F_T$  = Total gas flow (ml)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

**Induction:** Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

**Maintenance:** Surgical levels of anesthesia may be sustained with a 1.0-2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5% to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

**HOW SUPPLIED:** FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 ml amber-colored bottles.

**Storage:** Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

Revised 1-83

## Anaquest Forane® (isoflurane)

Anaquest  
 2005 West Beltline Highway  
 Madison WI 53713 2318  
 608 273 0019  
 Telex 910 286 2792  
 A Division of BOC Inc

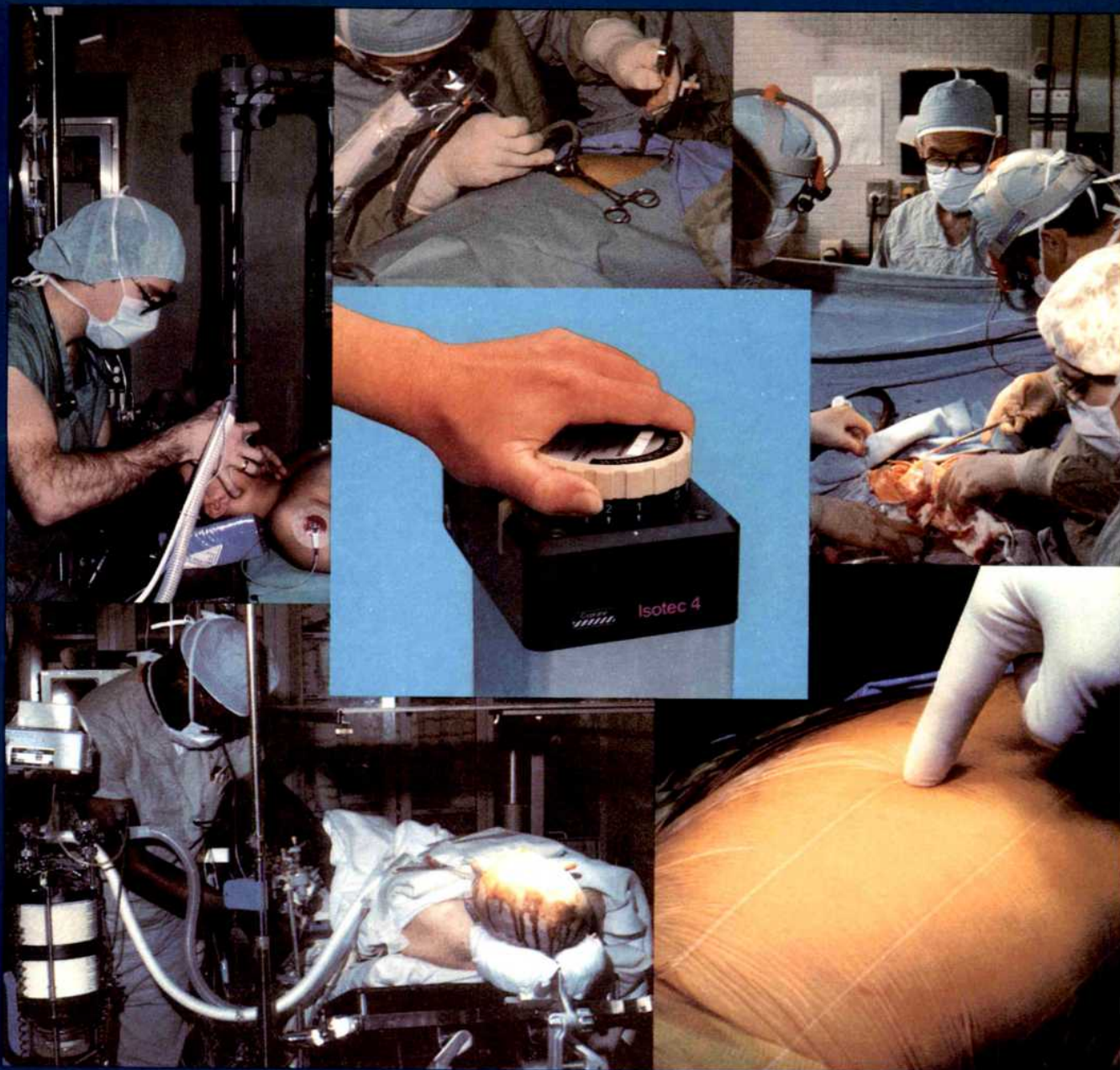
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# Forane<sup>®</sup> (isoflurane) The Versatile Anesthetic



**Anaquest**

Forane<sup>®</sup> (isoflurane)

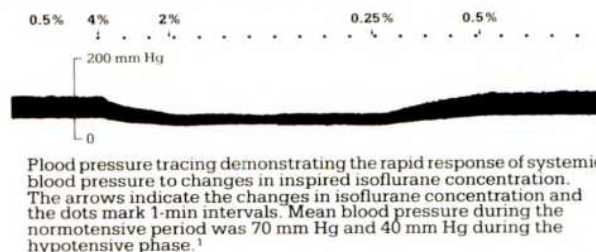




# Forane® (isoflurane) The Versatile Anesthetic

## A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.<sup>1</sup>



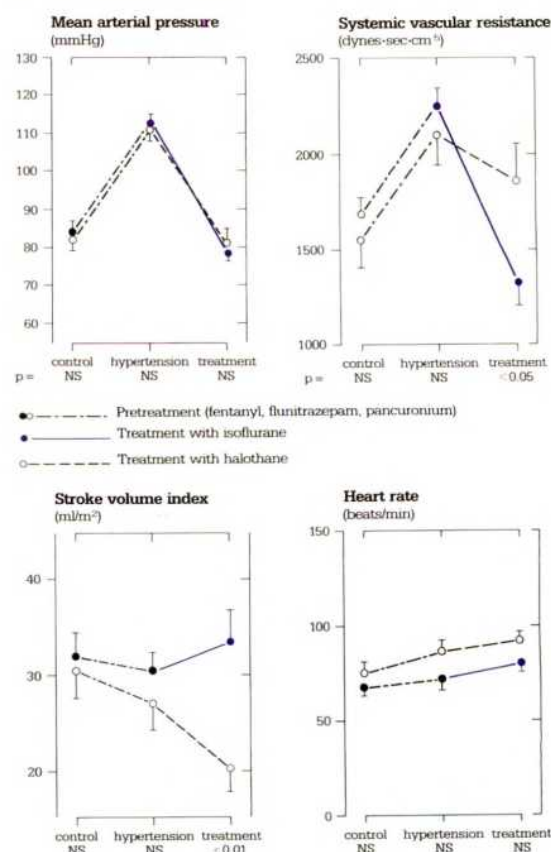
## Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when  $\text{PaCO}_2$  is controlled at 25-30 torr, and ICP may be readily lowered during surgery by decreasing  $\text{PaCO}_2$ .<sup>2</sup>

## Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery. (Adapted from Hess et al<sup>3</sup>).



## Potential of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).<sup>4,5</sup> Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

## Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."<sup>6</sup>

## A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."<sup>7</sup> (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.<sup>8</sup>

Post-laparoscopy Nausea (N) and Vomiting (V)		
Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N <sub>2</sub> O, O <sub>2</sub>	37	23 (62%)*
isoflurane, fentanyl, O <sub>2</sub>	20	6 (30%)
isoflurane, O <sub>2</sub>	20	5 (25%)

Adapted from Alexander et al<sup>8</sup> \*p<0.05

### References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. *Anesth Analg* 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. *Anesthesiology* 54:97-99, 1981.
3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. *Anesth Analg* 62:15-20, 1983.
4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. *Anesthesiology* 35:509-514, 1971.
5. Tracrium<sup>®</sup> (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709.
6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? *Anesth Analg* 60(9):666-682, 1981.
7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981.
8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. *Anesth Analg* 63:175, 1984.

For complete use information, please see following page.

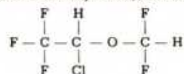
**Forane<sup>®</sup> ...a product of original Anaquest research**  
(isoflurane)



# Forane®...The Versatile Anesthetic (isoflurane)

**CAUTION:** Federal Law Prohibits Dispensing without Prescription

**DESCRIPTION:** FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Some physical constants are:

Molecular weight	184.5
Boiling point 760 mm Hg	48.5°C (Uncorr.)
Refractive index $n_D^{20}$	1.2990—1.3005
Specific gravity 25°/25°C	1.496
Vapor pressure in mm Hg **	
20°C	238
25°C	295
30°C	367
35°C	450

\*\*Equation for vapor pressure calculation:

$$\log_{10} P_{\text{vap}} = A + \frac{B}{T} \quad \text{where: } A = 8.056 \\ B = -1664.58 \\ T = ^\circ\text{C} + 273.16 \text{ (Kelvin)}$$

Partition coefficients @ 37°C

Water/gas	0.61
Blood/gas/gas	1.43
Oil/gas	90.8

Partition coefficients @ 25°C—rubber and plastic

Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinylchloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5

Purity by gas chromatography

Lower limit of flammability in oxygen

or nitrous oxide at 9 joules/sec

and 23°C

Lower limit of flammability in oxygen

or nitrous oxide at 900 joules/sec

and 23°C

Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

**CLINICAL PHARMACOLOGY:** FORANE (isoflurane) is an inhalation anaesthetic. The M.A.C. (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N <sub>2</sub> O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation of tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a high response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO<sub>2</sub>, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 ml of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

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undergoing abortions.

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**HOW SUPPLIED:** FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 ml amber-colored bottles.

**Storage:** Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

Revised 1-83

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# Soothing news for busy anesthesiologists

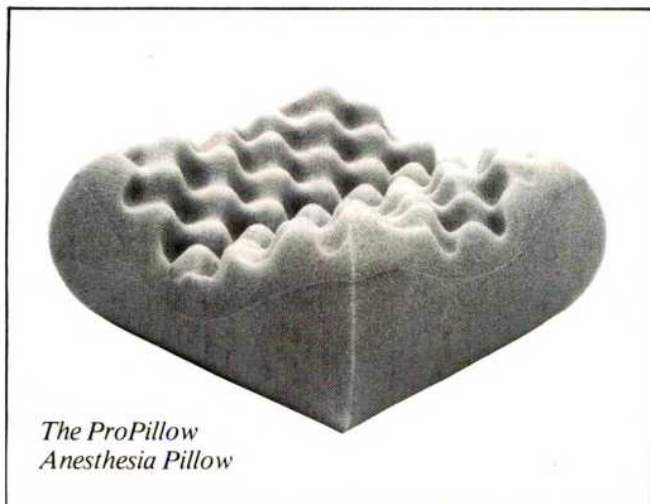
Dr. Smith was having another busy day in surgery. One Swan-Ganz placement had been unusually time-consuming. Plus the patient had been difficult to intubate. To top it off, the pump time had been excessive.

Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

But these two stories don't end here. About 28 days later, *both patients had a bald spot about the size of a silver dollar at the occiput. . . exactly where their heads were resting on the table for hours on end.* They were each advised by their surgeons that they had a 50% chance of their hair growing back within the next year. But there was an equal chance that their hair wouldn't grow back at all. The anesthesiologists on both cases were never told of the problem.

## **The ProPillow takes the pressure off**

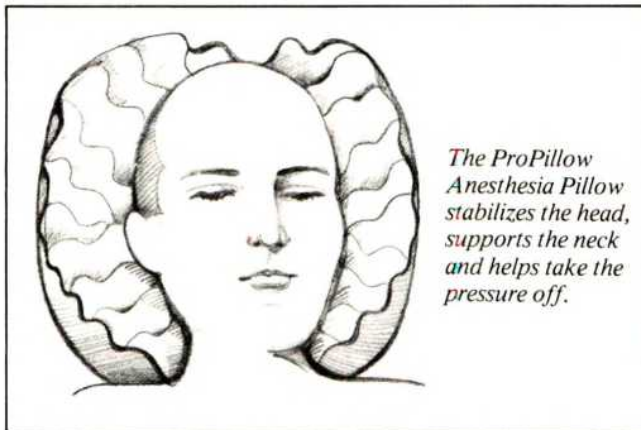
The ProPillow Anesthesia Pillow helps "take off the pressure" to the circulation of the face and scalp during prolonged anesthesia. It's unique "hills and valleys" construction creates a protective effect by evenly distributing the weight of the head and neck. Result: no more pressure in one area greater than any other area. And those precipitous swings in blood pressure are less likely to result in ischemia to the scalp. All this lessens the chance of post-op alopecia.



*The ProPillow  
Anesthesia Pillow*

## **The end of the juggling act**

The ProPillow lets you off gracefully from attempts to juggle the heavy head (10 lbs.) during intubation. The ProPillow Anesthesia Pillow stabilizes (by gently gripping) the patient's head in the neutral, "sniffing", position. It even helps free up one of your hands when you're using a mask for short cases.



*The ProPillow  
Anesthesia Pillow  
stabilizes the head,  
supports the neck  
and helps take the  
pressure off.*

## **An eye for details**

Awake patients really appreciate the comfort of the ProPillow Anesthesia Pillow. Especially the eye patients who are undergoing removal of cataracts with intra-ocular lens implants. And the ProPillow fits inside the frame used by Ophthalmologists during this tedious microsurgery. Less squirming. . . and possibly sedation required.

## **And the price is right**

Because of the ProPillow's reasonable price, some say we should call it disposable. But it is made to last for up to 50 cases. You can use a nurse's bouffant cap to cover the ProPillow. Or even spot wash and air-dry it. It's made from a bright blue, breathable, resilient polyurethane foam that's 100% non-allergenic and non-irritating to skin.

It's easy to order the ProPillow Anesthesia Pillow! Call us **TOLL FREE at (800) 227-0517 outside California**, or **(800) 554-5541 inside California**. Or, give this page to your head nurse or purchasing agent to get the ProPillow promptly. We ship within 24 hours. \*Pediatric Size available, ask for details.

**ProTechPacific**  
**1221 Andersen Drive**  
**San Rafael, CA 94901**

Makers of the ProPillow Anesthesia Pillow, NECK-PIL-O Neck Support Pillow, DIXEY Hip Abduction pillow and the new STRAPEZE \*Velcro Endotracheal Tube stabilizer.



# for prolonged procedures:

Mastectomy

Coronary Bypass

Hysterectomy

## **prolonged action can be a plus.**

Premedication with Ativan® (lorazepam) Injection may well be the most logical choice for longer surgical procedures where extended sedation and/or lack of recall are especially desirable.

A single injection of Ativan Injection provides dependable sedation for 6-8 hours. When surgery runs longer than anticipated, or unexpected delays occur, repeated injections may not be required.



Hip Replacement

Cholecystectomy

Knee Surgery

Head and Neck

Administered as recommended, Ativan Injection allays preoperative apprehension, relieves anxiety, leaves patients calm but cooperative and diminishes recall of events surrounding surgery. There is little, if any, IV irritation at proper dilution, and only minimal effects on blood pressure, pulse or respiratory rate.

The dosage of Ativan® (lorazepam) Injection should be individualized for each patient. For those in whom reduced recall and excellent sedation are desired, doses of 0.05 mg/kg up to a maximum of 4 mg should be administered. For patients in whom lack of recall is not desired, and for the elderly or debilitated, the dose should be reduced.



**ATIVAN**® (LORAZEPAM) ©  
**INJECTION** IM or IV

**Wyeth Laboratories**  
Philadelphia, PA 19101

See important information on following page.

# ATIVAN® (LORAZEPAM) INJECTION IM or IV

**DESCRIPTION:** Ativan® (lorazepam) injection, a benzodiazepine with anxiolytic and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

**CLINICAL PHARMACOLOGY:** IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose-related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

**INDICATIONS AND USAGE:** In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

**CONTRAINDICATIONS:** Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

**WARNINGS:** PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

**Pregnancy:** LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chloridiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

**Endoscopic Procedures:** There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

**PRECAUTIONS: General:** Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE AND ADMINISTRATION.) When lorazepam is used IV as premedication prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

**Information for Patients:** As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedication that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

**Laboratory Tests:** In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

**Drug Interactions:** Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

**Drug/Laboratory Test Interactions:** No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

**Pregnancy:** Pregnancy Category D. See WARNINGS section.

**Labor and Delivery:** There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

**Nursing Mothers:** Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

**Pediatric Use:** There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

**ADVERSE REACTIONS: CNS:** Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE AND ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were usually self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (later seen most commonly when scopolamine given concomitantly as premedication). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

**Local Effects:** IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately postinjection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

**Cardiovascular System:** Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

**Respiratory System:** Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

**Other Adverse Experiences:** Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

**DRUG ABUSE AND DEPENDENCE:** As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

**OVERDOSAGE:** Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

**DOSAGE AND ADMINISTRATION:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

**Intramuscular Injection:** For designated indications as premedication, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedications, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure. Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

**Intravenous Injection:** For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure. EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

**Administration:** When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

**HOW SUPPLIED:** Ativan® (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.  
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

For IM or IV injection.

Protect from light. Keep in refrigerator.

**Directions for Dilution for IV Use:** To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

**Wyeth Laboratories**  
Philadelphia, PA 19101



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For Improved Techniques and Successful Diagnoses...

# Basic Physics and Technology of Medical Diagnostic Ultrasound

**Matthew Hussey, Ph.D.**, Head, Department of Physics,  
Dublin Institute of Technology, Dublin, Ireland

**Basic Physics and Technology of Medical Diagnostic Ultrasound** introduces the clinician to the technology of ultrasound, with an emphasis on the roles physics and instrumentation play in diagnosis. Understanding of the principles discussed in this book can lead to:

- \* more thorough and fruitful diagnoses
- \* informed, critical evaluation of new technologies
- \* more efficient expenditures of health care resources

This highly readable book begins with a summary of the clinical applications of diagnostic ultrasound and a discussion of the role of this modality in the battery of diagnostic techniques currently available to the clinician. The basic features of ultrasound propagation and the various imaging techniques (A-Mode, M-Mode, static and dynamic B-Mode, Doppler) are then discussed extensively.

Because hard copy of the ultrasound image is of primary importance to the clinician, a special chapter on the methods of photography and the potential of electronic image recording is included.

Physicians using diagnostic ultrasound, radiographers, and medical or nursing students will find that **Basic Physics and Technology of Medical Diagnostic Ultrasound** is essential reading for a better understanding of the role of ultrasound in medicine.

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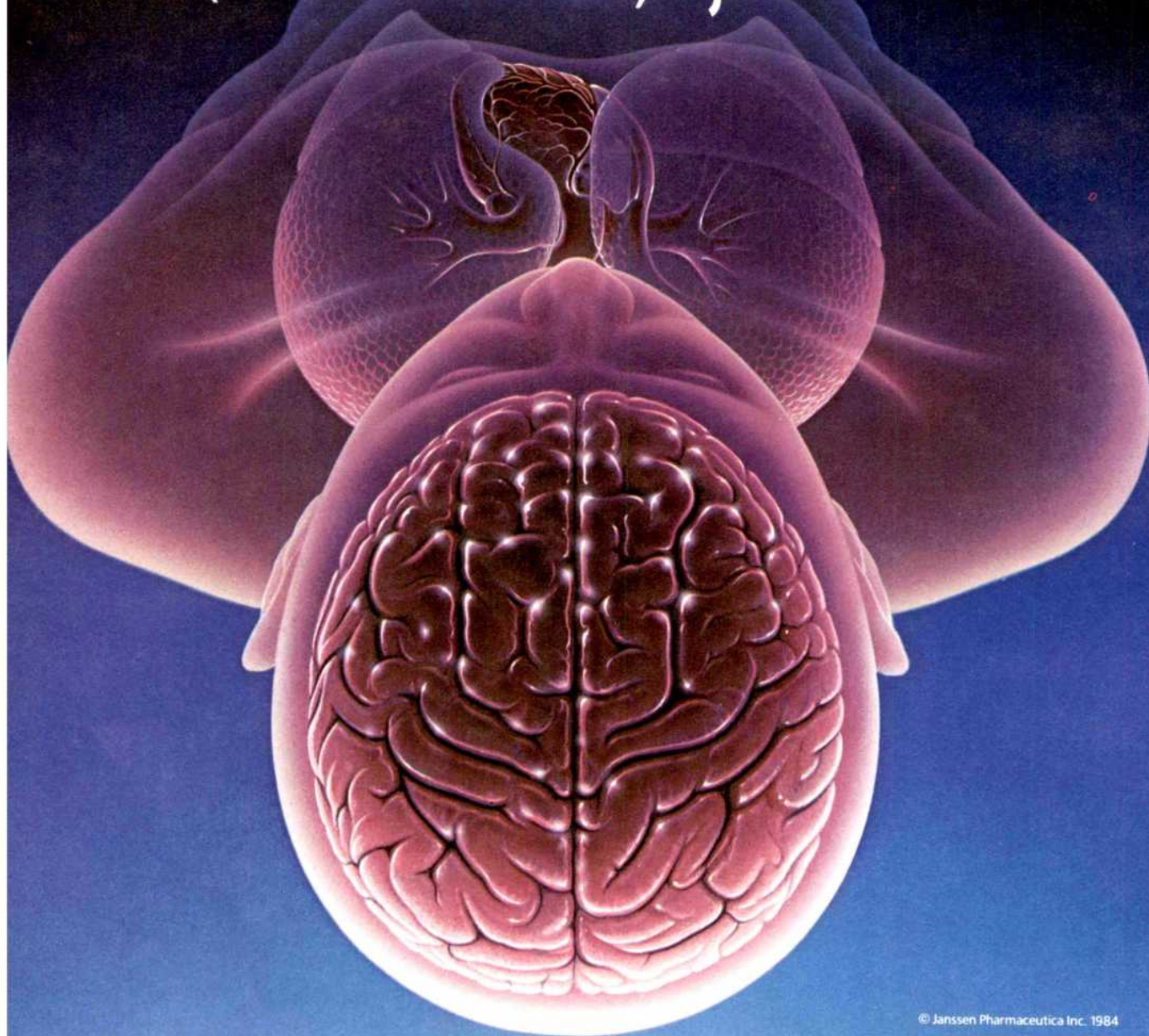


ANESTHESIA RECORD

SUMMARY OF PRE-OPERATIVE FINDINGS		SEX	RACE	AGE	WEIGHT	HABITUS	TEETH
BP 128/90	HR 97/80/	F		40	52.5 kg		upper & partial lower denture
HGB HCT	URINALYSIS	OTHER LAB DATA		FOOD INTAKE			
12.7/37.6	1.09 p 45.0 It ketones			NPO			
Malignant Melanoma				yes			

*A Case for  
More Predictable Control*

**SUFENTA<sup>®</sup>**  
(sufentanil citrate) Injection **CII**



*...More Predictable Control  
from Induction through Recovery*

## **COMPARED WITH ISOFLURANE<sup>\*1,2</sup>**

- Superior hemodynamic stability
- Shorter recovery times
- Better maintenance of postoperative analgesia
- Lower total cost per procedure

\*In a comparative study<sup>1,2</sup> of patients undergoing major orthopedic surgery who received either SUFENTA-N<sub>2</sub>O (n=10) or isoflurane-N<sub>2</sub>O (n=10).

1. Scientific Exhibit, Sufentanil vs. Isoflurane in Major Orthopedic Procedures (Fahmy NR, Principal Investigator), March 1983.

2. Fahmy NR, Beemer GH, Roberts JT: Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

## **COMPARED WITH FENTANYL<sup>3,4</sup>**

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- Faster, more comfortable recovery
- More effective blocking of surgical stress response
- Superior hemodynamic stability
- Smaller volume of injection
- Lower total cost per procedure

3. Smith NT, Dec-Silver H, Harrison WK, et al: ASA Abstract, Anesthesiology (Suppl) 57: A291, 1982.

4. Flacke JW, Bloor BC, Flacke WE, et al: Comparative Effects of Sufentanil and Fentanyl Versus Meperidine and Morphine in Balanced Anesthesia. Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

For complete Product Information, please see next page.

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# SUFENTA<sup>®</sup>

## (sufentanil citrate) Injection

**CAUTION:** Federal Law Prohibits Dispensing Without Prescription

### DESCRIPTION

SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienylethyl)-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1). SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-7.5.

### CLINICAL PHARMACOLOGY

SUFENTA is an opioid analgesic. SUFENTA is approximately 5 to 7 times as potent as fentanyl. (Dosage requirements for equianalgesic effect will be 1/5-1/7 those of fentanyl on a mg/kg basis.) At doses of up to 8 µg/kg, SUFENTA provides profound analgesia; at doses ≥8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 0.72 minutes, redistribution of 13.7 minutes and an elimination half-life of 148 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl. At dosages of ≥2.6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable low heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of fentanyl.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given induction agents.

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

### INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated:

as an analgesic adjunct at dosages of up to 8 µg/kg in the maintenance of balanced general anesthesia, as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

### CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

### WARNINGS

**SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.**

**An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.**

SUFENTA may cause skeletal muscle rigidity particularly of the truncal muscles. The incidence can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg; 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion; or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

### PRECAUTIONS

The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

**Head Injuries:** SUFENTA may obscure the clinical course of patients with head injuries.

**Impaired Respiration:** SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

**Impaired Hepatic or Renal Function:** In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

**Drug Interactions:** An additive effect with SUFENTA may be exhibited in patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

**Pregnancy Category C:** SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman. **Pediatric Use:** The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

**Animal Toxicology:** The intravenous LD<sub>50</sub> of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

### ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia

Gastrointestinal: nausea, vomiting

Respiratory: apnea, postoperative respiratory depression, bronchospasm

Dermatological: itching

Central Nervous System: chills

Miscellaneous: intraoperative muscle movement

### DRUG ABUSE AND DEPENDENCE

SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

### OVERDOSAGE

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD<sub>50</sub> of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD<sub>50</sub>s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

### DOSSAGE AND ADMINISTRATION

The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

**Usage in Children:** For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg/kg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

**Premedication:** The selection of preanesthetic medications should be based upon the needs of the individual patient.

**Neuromuscular Blocking Agents:** The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSSAGE RANGE CHART	
TOTAL DOSSAGE	MAINTENANCE DOSSAGE
<b>1-2 µg/kg:</b> administered with nitrous oxide oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	<b>10-25 µg (0.2-0.5 ml):</b> as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.
<b>2-8 µg/kg:</b> administered with nitrous oxide oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	<b>25-50 µg (0.5-1 ml):</b> as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.
<b>8-30 µg/kg:</b> (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	<b>25-50 µg (0.5-1 ml):</b> as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

### HOW SUPPLIED

SUFENTA (sufentanil citrate) injection for intravenous use is available as:

NDC 50458-050-01 50 µg/ml 1 ml ampoules in packages of 10

NDC 50458-050-02 50 µg/ml 2 ml ampoules in packages of 10

NDC 50458-050-05 50 µg/ml 5 ml ampoules in packages of 10

Protect from light. Store at room temperature.



**JANSSEN**  
PHARMACEUTICA

Piscataway, N.J. 08854

7618500

U.S. Patent No. 3,998,834  
May 1984



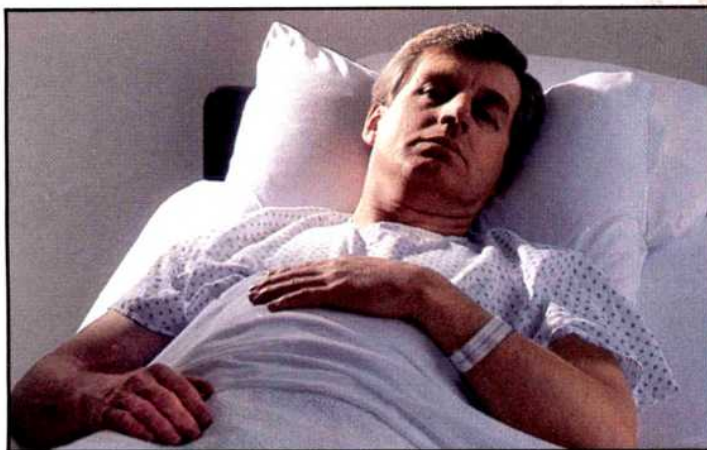
# CALM AND COOPERATIVE THROUGHOUT THE PROCEDURE

## Maximal control of anxiety

Within minutes,<sup>1,2</sup> the potent calming action of Injectable Valium (diazepam/Roche) administered I.V. begins to control intense pre-endoscopic anxiety. Patients are soon relaxed, yet able to follow simple instructions. While recovery to alertness is usually smooth and predictable, patients should be advised against driving or engaging in other hazardous activities.

## Minimal recall

Amnesic effects also start within minutes and generally last 20 to 60 minutes.<sup>2-6</sup> Most patients have diminished recall—or no recall at all—of their endoscopy. Use with extreme care in elderly and very ill patients and in those with limited pulmonary reserve. Resuscitative facilities should be readily available and narcotic dosage reduced by at least one-third or, in some cases, eliminated.



*Injectable*  
**VALIUM<sup>®</sup> IV**  
*diazepam/Roche<sup>®</sup>*

In the moments before endoscopy



Please see references and summary of product information on the next page.  
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**References:** 1. Diazepam and lorazepam in anesthesia. *Drug Ther Bull* 17(5): 19-20, Mar 2, 1979. 2. Conner JT, et al: *J Clin Pharmacol* 18:285-292, May-Jun 1978. 3. George KA, Dundee JW: *Br J Clin Pharmacol* 4:45-50, Feb 1977. 4. Dundee JW, Pandit SK: *Br J Pharmacol* 44:140-144, Jan 1972. 5. Dundee JW, et al: *Br J Anaesth* 51:439-446, May 1979. 6. Gregg JM, Ryan DE, Levin KH: *J Oral Surg* 32:651-664, Sep 1974.

# Injectable VALIUM® diazepam/Roche

**Before prescribing, please consult complete product information, a summary of which follows:**

**Indications:** Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

**Contraindications:** Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

**Warnings:** To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least 1/3, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

**Usage in Pregnancy:** Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

**Precautions:** Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), i.e., phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use

## Injectable Valium® (diazepam/Roche)

topical anesthetic, have necessary countermeasures available. Hypotension, muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed by association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

**Adverse Reactions:** Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoaesthesia, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor changes, usually low-voltage fast activity, of no known significance.

**Dosage:** Usual initial dose in older children and adults is 2 to 20 mg I.M., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (2 to 5 mg) with slow dosage increase for elderly or debilitated patients when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

**I.M. use:** by deep injection into the muscle.

**I.V. use:** inject slowly, take at least one minute for each 5 mg (1 ml) given. Use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., in 3 to 4 hours if necessary; acute alcohol withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, administer I.V. slowly; for tetanus in infants 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred) 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals 30 mg maximum. Repeat in 2 to 4 hours if necessary, keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful in endoscopic procedures, titrate I.V. dosage to desired sedative response, usually 10 mg or less but up to 20 mg (if narcotics are omitted) immediately to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be given oral form if further treatment is required.

**Management of Overdosage:** Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value. **Supplied:** Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (posable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.



Manufactured by Hoffmann-La Roche Inc.  
Nutley, New Jersey 07110

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**The Anectine Flo-Pack®** needs no refrigeration and mixes instantly with diluent. No separate needle or syringe is necessary. And, both the 500 and 1000 mg sizes work equally well with either bottles or bags.

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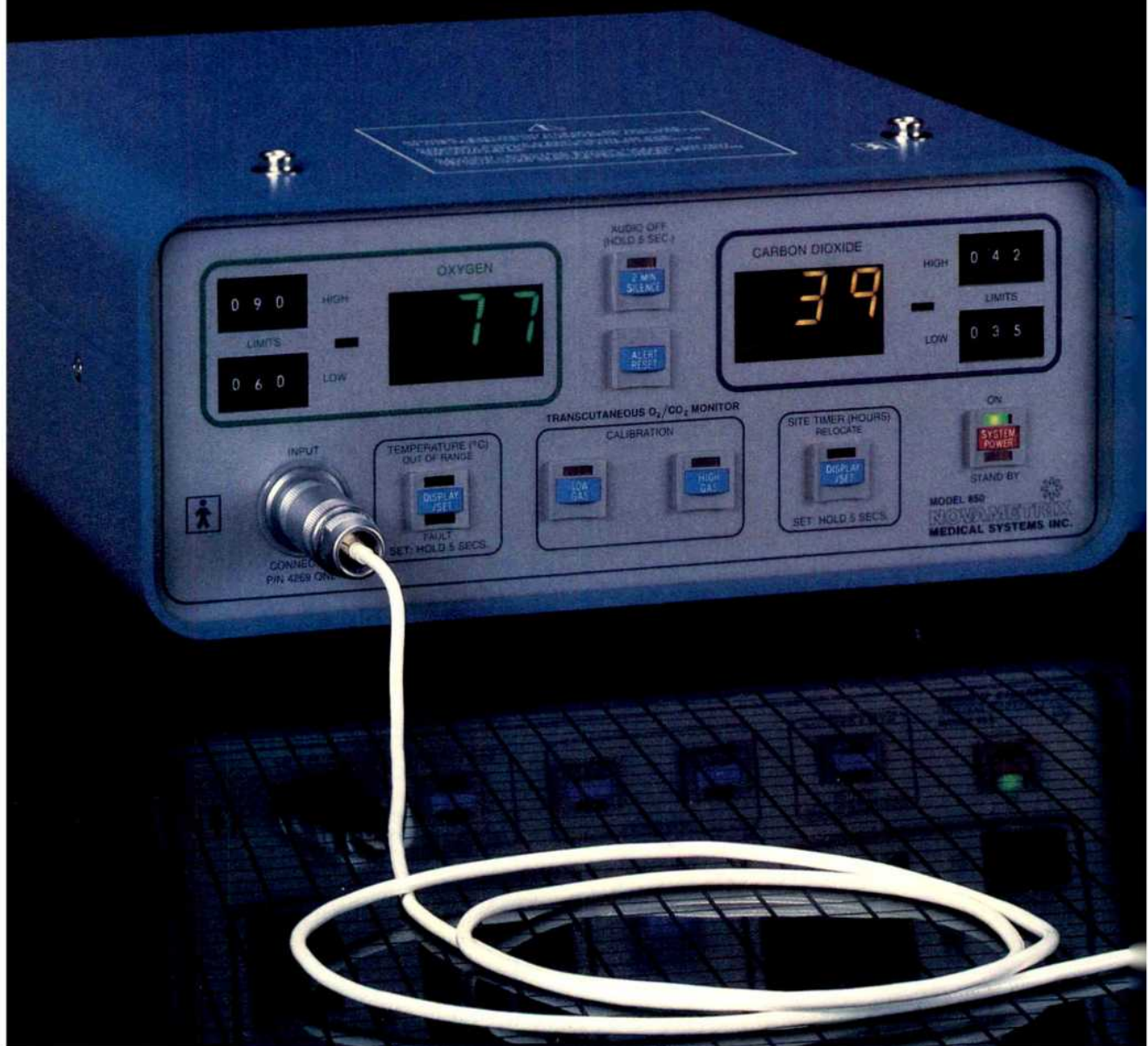
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Relax. With Novametrix you can have both. In one simple and surprisingly inexpensive package. Because when you assemble a transcutaneous monitoring system that's built around the MODEL 850 monitor and our CO<sub>2</sub>MMO<sub>2</sub>N SENSOR™ O<sub>2</sub>/CO<sub>2</sub> electrode, you get the ultimate in performance and convenience. From the company that's designed, built, and sold more transcutaneous monitors than any other.

The MODEL 850 is a dual function monitor featuring simultaneous displays of transcutaneous O<sub>2</sub> and CO<sub>2</sub>, and packed with more monitoring capability and clinical options than we've ever offered in a bedside unit that's also portable. Our exclusive CO<sub>2</sub>MMO<sub>2</sub>N SENSOR offers O<sub>2</sub> and CO<sub>2</sub> sensing from a single sensor site, to save you time and simplify patient management.

Unlike some other dual function sensors, the CO<sub>2</sub>MMO<sub>2</sub>N SENSOR features two separate electrode systems in one small-but-rugged sensor body. So you get faster response and minimal drift.

But perhaps the best thing about the MODEL 850 and CO<sub>2</sub>MMO<sub>2</sub>N SENSOR is their complete compatibility with other Novametrix equipment you may already own or anticipate.

Fact is, there's no reason to take a chance with another company. Because for state-of-the-art features, dual O<sub>2</sub>/CO<sub>2</sub> function/one-site convenience, and unmatched reliability, all you need to do is look to the leader.

# We make it simple.



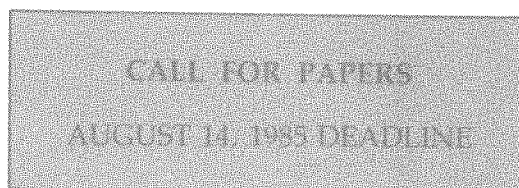
Sensor shown larger than actual size.



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# MarCaine<sup>®</sup> Spinal

bupivacaine HCl, USP, 0.75%  
with dextrose, USP, 8.25% injection

## PLEASE CONSULT FULL PRESCRIBING INFORMATION: A SUMMARY FOLLOWS:

**CONTRAINDICATIONS:** MARCAINE Spinal is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type. The following conditions preclude the use of spinal anesthesia: (1) Severe hemorrhage, severe hypotension, or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output; (2) Local infection at the site of proposed lumbar puncture; (3) Septicemia.

**WARNINGS:** LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL-VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS AND PRECAUTIONS.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Spinal anesthetics should not be injected during uterine contractions, because spinal fluid current may carry the drug further cephalad than desired.

A free flow of cerebrospinal fluid while performing spinal anesthesia indicates entry into the subarachnoid space. Aspiration should be performed before the anesthetic is injected to confirm entry into the subarachnoid space and to avoid intravascular injection.

MARCAINE solutions containing epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because severe, persistent hypertension may occur. MARCAINE solutions containing a vasoconstrictor such as epinephrine should be used cautiously in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Administration of MARCAINE to patients younger than 18 years is not recommended, nor is the mixing or the prior or concurrent use of any other local anesthetic with MARCAINE because of insufficient data on the clinical use of such mixtures.

**PRECAUTIONS: General:** The safety and effectiveness of spinal anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS.) The patient's should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used. Aspiration for blood should be performed before injection and injection should be made slowly. Tolerance varies with the status of the patient. Elderly patients and acutely ill patients may require reduced doses. Reduced doses may also be indicated in patients with increased intra-abdominal pressure (including obstetrical patients), if otherwise suitable for spinal anesthesia.

Cardiovascular and respiratory vital signs and the patient's state of consciousness after local anesthetic injection should be constantly and carefully monitored. Restlessness, anxiety, incoherent speech, light-headedness, numbness, and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Spinal anesthetics should be used cautiously in patients with severe disturbances of cardiac rhythm, shock or heart block.

Sympathetic blockade during spinal anesthesia may result in peripheral vasodilation and hypotension, the extent depending on the number of dermatomes blocked. Blood pressure should be carefully monitored especially in early phases of anesthesia. Hypotension may be controlled by vasoconstrictors in dosages depending on the severity of hypotension and response of treatment. The level of anesthesia should also be carefully monitored because it is not always controllable in spinal techniques.

Because the liver metabolizes amide-type local anesthetics such as MARCAINE, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used cautiously in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. However, dosage recommendations for spinal anesthesia are much lower than those in other major blocks; most experience regarding hepatic and cardiovascular disease dose-related toxicity is derived from these other major blocks.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are used in patients during or following the administration of potent inhalation agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be considered.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. It is not known whether amide-type local anesthetics trigger this reaction, and since the need for supplemental general anesthesia cannot be predicted in advance, a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome depends on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene. (Consult dantrolene sodium package insert before using.)

The following conditions may preclude the use of spinal anesthesia, depending on the physician's evaluation of the situation and ability to deal with possible complications or complaints: (1) Preexisting diseases of the central nervous system, such as those resulting from pernicious anemia, poliomyelitis, syphilis, tumor; (2) Hematologic disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage; (3) Chronic backache and preoperative headache; (4) Hypotension and hypertension; (5) Technical problems (persistent paresthesias or bloody tap); (6) Arthritis or spinal deformity; (7) Extremes of age. (8) Psychosis or other causes of poor cooperation by the patient.

**Information for Patients:** Patients should be informed that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the MARCAINE Spinal package insert.

**Clinically Significant Drug Interactions:** Local anesthetic solutions containing epinephrine or norepinephrine administered to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided but, when necessary, careful monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term studies in animals of most local anesthetics including bupivacaine to evaluate carcinogenic potential have not been conducted. Mutagenic potential or the effect on fertility have not been determined. There is no evidence from human data that MARCAINE Spinal may be carcinogenic, or mutagenic or that it impairs fertility.

**Pregnancy Category C:** Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered in doses comparable to 230 and 130 times respectively the maximum recommended human spinal dose. There are no adequate and well-controlled studies in pregnant women of bupivacaine's effect on the developing fetus. Bupivacaine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This does not exclude the use of MARCAINE Spinal at term for obstetrical anesthesia. (See Labor and Delivery.)

**Labor and Delivery:** Spinal anesthesia has a recognized use during labor and delivery. Bupivacaine hydrochloride, when administered properly, via the epidural route in doses 10 to 12 times the amount used in spinal anesthesia has been used for obstetrical analgesia and anesthesia without evidence of adverse effects on the fetus.

Regional anesthesia has produced maternal hypotension. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate should be monitored continuously and electronic fetal monitoring is highly advisable.

It is extremely important to avoid aortocaval compression by the gravid uterus during administrations of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and the gravid uterus displaced to the left.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. Obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may result in diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

Cardiac arrest has been reported during use of MARCAINE 0.75% solution for epidural anesthesia in obstetrical patients. The MARCAINE hydrochloride package insert for epidural, nerve block, etc., discusses this problem. These cases are compatible with systemic toxicity following unintended intravascu-

lar injection of the much larger doses recommended for epidural anesthesia and have not occurred within the dose range of bupivacaine hydrochloride 0.75% recommended for obstetrical spinal anesthesia. The 0.75% concentration of MARCAINE is therefore not recommended for obstetrical epidural anesthesia. MARCAINE Spinal (bupivacaine HCl 0.75% with dextrose 8.25%) is recommended for spinal anesthesia in obstetrics.

**Nursing Mothers:** It is not known whether local anesthetic drugs are excreted in human milk; therefore, caution should be exercised when local anesthetics are administered to a nursing woman.

**Pediatric Use:** Until further experience is gained in patients younger than 18 years, administration of MARCAINE Spinal in this age group is not recommended.

**ADVERSE REACTIONS:** Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. The most commonly encountered acute adverse experiences following spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or under-ventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site, or from unintentional intravascular injection of a local anesthetic solution. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

**Respiratory System:** Respiratory paralysis or underventilation may result from upward extension of the level of spinal anesthesia and may lead to secondary hypoxic cardiac arrest if untreated. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation may contribute to underventilation. This will usually occur within minutes of the injection of spinal anesthetic solution, but because of differing maximal onset times, intermittent drug use, and surgical manipulation, it may occur at any time during surgery or the immediate recovery period.

**Cardiovascular System:** Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunken blood and interstitial fluid volumes, cephalad spread of the local anesthetic and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias and possibly cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

**Central Nervous System:** Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia (see Respiratory System) and hypotension for the same reason (see Cardiovascular System) are the two most commonly encountered central nervous system-related adverse observations which demand immediate countermeasures.

High doses, or inadvertent intravascular injections may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.

**Neurologic:** Adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and also depend on the particular drug used, the route of administration and the physical status of the patient. Many effects may be related to local anesthetic techniques, with or without a contribution from the drug.

Neurologic effects following spinal anesthesia may include loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness and paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete or no recovery; hypotension; high or total spinal block; urinary retention; headache; backache; septic meningitis; meningismus; arachnoiditis; slowing of labor; increased incidence of forceps delivery; shivering; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid; fecal and urinary incontinence.

**Allergic:** Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions include urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptomatology (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported.

**Other:** Nausea and vomiting may occur during spinal anesthesia.

**OVERDOSAGE:** Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia due to relaxation of sympathetic tone or contributory mechanical obstruction of venous return.

**Management of Local Anesthetic Emergencies:** The first consideration is prevention through careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. Administer oxygen at the first sign of change.

The first step in managing systemic toxic reactions, as well as underventilation or apnea due to a high or total spinal is to immediately establish and maintain a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. A 50 mg to 100 mg bolus IV injection of succinylcholine will paralyze the patient without depressing central nervous or cardiovascular systems and facilitate ventilation. A bolus IV dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after instituting these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and when appropriate, a vasopressor dictated by the clinical situation.

Hypotension due to sympathetic relaxation may be managed with intravenous fluids, in an attempt to relieve mechanical obstruction of venous return or by using vasopressors and, if indicated, by giving plasma expanders or whole blood.

Endotracheal intubation, employing drugs and techniques familiar to the physician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in maintaining a patent airway or if prolonged ventilatory (assisted or controlled) support is indicated.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to a high or total spinal may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, standard cardiopulmonary resuscitative measures should be instituted and maintained for a prolonged period if necessary. Recovery has been reported after prolonged resuscitative efforts.

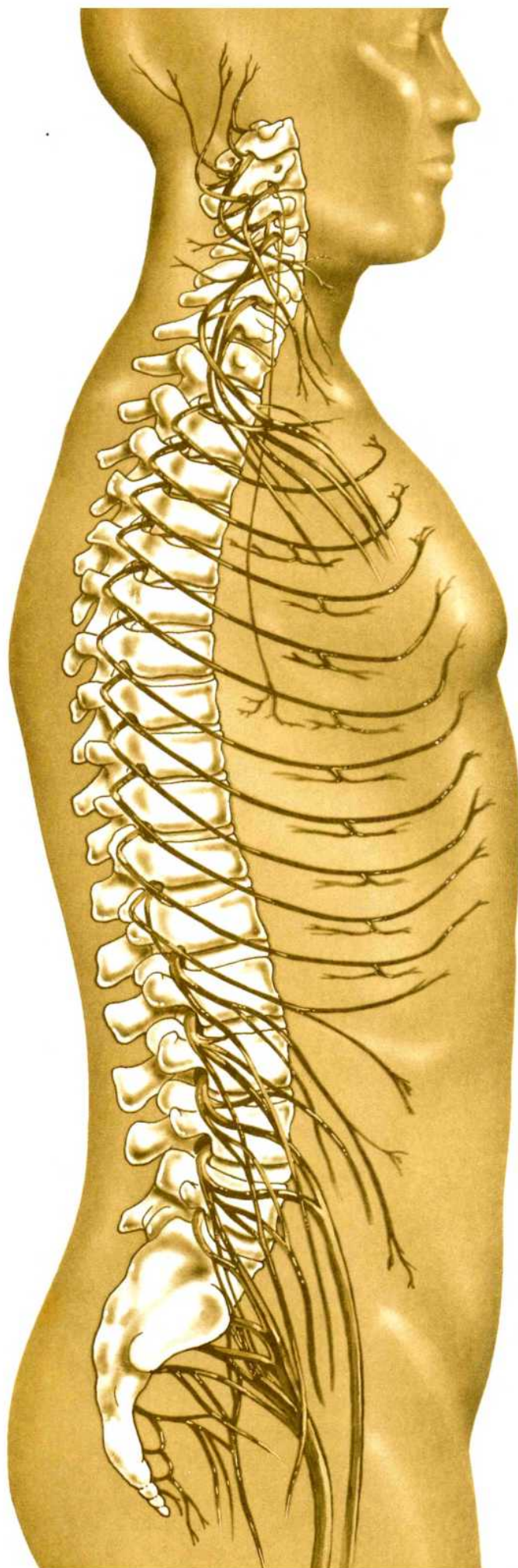
The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous LD<sub>50</sub> in mice is 6.5 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

**Composition of MARCAINE Spinal Solutions:** Each 1 mL of MARCAINE Spinal contains 7.5 mg bupivacaine hydrochloride and 82.5 mg dextrose. The pH of this solution is adjusted between 4.0 and 6.5 with sodium hydroxide or hydrochloric acid. The specific gravity of MARCAINE Spinal is between 1.030 and 1.035 at 25°C, and 1.03 at 37°C. MARCAINE Spinal does not contain any preservatives.

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**Reference:**

<sup>1</sup> Moore DC: Spinal anesthesia: Bupivacaine compared with tetracaine.  
*Anesth Analg* 1980; 59:743-750.

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## Editorial

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### Ever More Statistics

Nathan L. Pace, MD

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Avram et al. (1) have performed a very useful service for anesthesia researchers and anesthesia journals by evaluating statistical methods in the two primary American anesthesia journals. As reported in this issue of *Anesthesia and Analgesia*, 243 articles from 24 issues of the two journals for the years 1981 and 1983 were assessed for aspects of experimental design and statistical analysis. The experimental design of each article was evaluated for the use of a control group (if necessary) and for the random allocation of subjects to different treatment groups (if possible). Each article was also checked for errors in the use of descriptive, inferential, and correlative statistics. [Descriptive statistics describe the measured variables by calculated parameters (means and standard deviations). Inferential statistics compare the treatment groups for differences in the measured variables. Correlative statistics plot the relationship between number pairs (linear regression).] Specific findings included the following: 1) frequent failure (>60%) to allocate subjects randomly or to report adequately random allocation of subjects to different therapy groups; 2) a very high error rate (>80%) in the use of parametric inferential statistics; 3) no difference in the frequency of statistical errors between the two journals or between the years 1981 and 1983. This report joins other reviews cited by Avram et al. that found similar error rates in both clinical and research journals of other specialties.

There has been more than one editorial commenting on the need for higher standards of statistical excellence in anesthesia journals and in journals of other branches of medicine. Have the editorial exhortations of Glantz (2) and Longnecker (3) been for

naught? To the contrary, increased statistical sophistication is already being seen. To detect the improvement requires a broader perspective. For example, one of the most common errors, cited by both Glantz and Longnecker, has been the use of *t*-tests to look for differences among more than two groups. Proper statistical techniques for these comparisons include analysis of variance (ANOVA) and/or individual comparisons adjusted for the number of pairings (4,5).

I reviewed the December 1979 and December 1984 issues of *Anesthesia and Analgesia* and *Anesthesiology* to see if there is now more frequent use of ANOVA and adjusted individual comparison tests. Of the original and scientific articles analyzing continuous variables, each article was classified as using ANOVA and adjusted individual comparisons, or as using *t*-tests; no attempt was made to determine whether the statistical tests had been properly applied. It was evident that during the last five years (Table 1) most authors began using the more appropriate statistical tests (even if incorrectly) for the comparison of multiple groups.

What more should be done to respond to the findings of Avram et al.? Editorial boards might well consider the very specific recommendations of Altman (6,7) regarding statistical review during the editorial process. Researchers should review a recommended set of guidelines for contributors to medical journals (7) with particular thought given to the design of outcome studies. As a recent editorial by Roizen (8) pointed out, anesthetic drugs are usually compared by their effects on "process variables" such as blood pressure or urinary output. The specialty of anesthesia needs outcome studies that definitively resolve the purported and real merits of anesthetic drugs, techniques, and monitors.

What does all this mean to the clinician reader? Avram et al. express the hope that better statistical methods will not impair the understanding of the research report by the nonacademic anesthesiologist. Certainly physicians, by virtue of their selection pro-

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Table 1.

Journal issue	Number of articles reviewed	Use of parametric statistics	Use of ANOVA or adjusted individual comparisons	Use of simple <i>t</i> -tests
<i>Anesthesia and Analgesia</i> Nov/Dec 79	12	7	3 (43%)	4 (57%)
<i>Anesthesiology</i> Dec 79	9	8	2 (25%)	6 (75%)
<i>Anesthesia and Analgesia</i> Dec 84	11	10	7 (70%)	3 (30%)
<i>Anesthesiology</i> Dec 84	15	12	11 (92%)	1 (17%)

1979 vs 1984—Mantel-Haenszel  $\chi^2 = 6.60$ ;  $P = 0.0102$ .

*Anesthesia and Analgesia* vs. *Anesthesiology*—Mantel-Haenszel  $\chi^2 = 0.00$ ;  $P = 0.9908$ .

cess, have the intelligence to understand the elementary statistical principles misused most frequently. The physician has a sufficient background in arithmetic, algebra, and abstract reasoning to master the methods of experimental design and statistical analysis in most research. Yet in my experience most clinician readers have an intellectual disuse atrophy about mathematics in general and statistics in particular. I find few who even understand the calculation of or interpretation of standard deviations and standard errors.

Though mathematics and its branch, statistics, are the language of science, they can be dreadfully dull. But if an anesthesiologist is to be a practitioner of scientific medicine rather than a cookbook technician, he must at least read the language of science so that he can independently assess and interpret the scientific report. Obviously, the researcher must both speak and read the language of science. Without some basic fluency in statistics as a second language necessary for professional life, the increased sophistication of statistical methods will turn journals into a

Tower of Babel. The journals and societies of anesthesia can and must help the clinician relearn these forgotten skills.

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## Sex Differences in Halothane Metabolism and Hepatotoxicity in a Rat Model

John L. Plummer, PhD, Pauline de la M. Hall, FRCPA, Mark A. Jenner, BSc, and Michael J. Cousins, MD

PLUMMER JL, HALL DE LA M. P, JENNER MA, COUSINS MJ. Sex differences in halothane metabolism and hepatotoxicity in a rat model. *Anesth Analg* 1985;64:563-9.

*This study was designed to investigate sex differences in halothane metabolism and hepatotoxicity in the hypoxic rat model. Phenobarbital-induced male and female rats were anesthetized with 1% halothane in 14% oxygen for two hours. Female rats were found to metabolize halothane by the oxidative pathway to a similar extent as males, but the extent of metabolism by the reductive pathway was less in females. All male rats exposed under these conditions de-*

*veloped confluent centrilobular hepatic necrosis. Females were less susceptible than males to the hepatotoxic effect of halothane, with responses ranging from no hepatic injury to confluent centrilobular necrosis limited to within a few cells of the central veins. This lesser susceptibility was not, however, solely due to the lesser extent of reductive metabolism in females, as lowering the inspired oxygen concentration to 12% increased the extent of reductive metabolism but did not increase the severity of the hepatic injury.*

**Key Words:** ANESTHETICS, VOLATILE—halothane. BIOTRANSFORMATION (DRUG)—halothane. LIVER, TOXICITY—halothane.

Massive hepatic necrosis is a rare complication of halothane anesthesia. This complication is more commonly reported in females than in males (1). In most case series, however, the proportion of females in the population from which the cases were obtained (i.e., those patients who received halothane and would have been included in the study had they developed halothane hepatitis) is unknown, and so the preponderance of female cases may not imply that female sex is a risk factor. Nevertheless, the consistency of results among different studies carried out at different times and in different locations has led to the common notion that females are more likely to develop hepatitis after halothane than are males.

In contrast, studies using the hypoxic rat model, in which males consistently develop hepatic centrilobular necrosis after halothane, have shown female rats to be less susceptible to halothane hepatotoxicity (2). The hypoxic rat model has been a valuable tool for investigation of mechanisms of, and factors influ-

encing, halothane hepatotoxicity. The extent to which information gained in the rat model can be applied to humans is largely dependent on the similarity of mechanisms in the model and humans. Thus if the sex difference observed in the rat model, but not in humans, is due to a fundamental difference in mechanisms, the utility of the rat model would be severely limited. It appeared possible, however, that the lesser severity of halothane hepatotoxicity in female rats compared to males could be due to a lesser extent of metabolism of halothane to toxic intermediates. Such a sex difference in hepatic metabolism has been well-documented for a number of drugs (3). Although there is also evidence of sex differences in drug metabolism in humans (4), these differences are not as great as in the rat.

### Methods

#### *Animals*

Fischer 344 rats were used in all experiments. The ages of the animals ranged from 82-92 days, and weights ranged from 102-178 g (mean, 143 g) for females and 186-274 g (mean, 219 g) for males. When phenobarbital (PB) induction was required, it was brought about by addition of sodium phenobarbital, 1 g/L, to the drinking water for seven days, followed

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by one day of tap water prior to the experiment. Within each experiment and each sex, assignment of rats to treatments was by lottery.

### *Sex Difference in Halothane Metabolism and Hepatotoxicity*

Male and female rats were assigned to receive PB induction plus halothane-hypoxia ( $n = 3$  animals of each sex), PB induction plus hypoxia ( $n = 2$  animals of each sex), or no treatment ( $n = 2$  animals of each sex). This experiment was replicated four times to provide sufficient independent measurements of volatile metabolite exhalation for statistical analysis.

Anesthesia was induced with 2% halothane-14% oxygen for 2 min, after which male and female rats were anesthetized simultaneously in separate multiport glass anesthetic masks designed to permit collection of exhaled breath (5). Anesthesia was maintained for 2 hr with 1% halothane-14% oxygen-balance nitrogen. The hypoxic gas mixture was split into three streams. Two streams were passed through Fluotec M K III vaporizers and then to the anesthetic masks, one containing male and the other female rats, at flow rates of 2.5 L/min to each mask. Halothane concentrations in the fresh gas flow to each mask were monitored with an LB2 Medical Gas Analyzer (Beckman) and maintained in the range 0.98-1.02%. Body temperature of the anesthetized animals was maintained by placing them on an electric blanket heated to 32°C. The third hypoxic gas stream did not pass through a vaporizer but was passed directly into a plastic chamber of approximately 80 L volume, in which animals assigned to receive hypoxia but no halothane were placed.

After 15, 35, 55, 75, 95 and 115 min of anesthesia, fresh gas flow to the anesthetic masks was turned off for 30 sec and pooled breath samples (12.5 ml) were collected by glass syringe from each mask. Breath samples were analyzed for the volatile halothane metabolites, 2-chloro-1,1,1-trifluoroethane (CTF) and 2-chloro-1,1-difluoroethylene (CDF) and halothane by gas chromatography (Carbowax 400, 90°). On some occasions, a Centronics MGA 200 Medical Gas Analyzer was used to measure carbon dioxide in the pooled breath samples, and these values were compared to those measured in the end-expired breath collected by placing the gas analysis probe in the nostril of individual animals during anesthesia.

At the end of each experiment, animals were placed in plastic metabolic cages. Urine was collected for 22 hr, after which animals were stunned, decapitated, and blood and liver tissue were taken.

### *Effect of PB Induction on Halothane Metabolism*

In order to assess the effects of PB induction in each sex, six rats of the same sex were assigned to receive either PB induction plus 2 hr of halothane-hypoxia ( $n = 3$ ) or halothane-hypoxia without PB induction ( $n = 3$ ). Animals were treated as described above. This experiment was replicated three times for each sex, giving a total of nine PB-induced and nine un-induced animals of each sex.

A further experiment was carried out to investigate the effect of decreasing inspired oxygen concentration to below 14% in female rats only. Ten PB-induced female rats were anesthetized in two masks, five animals in each mask. The animals in one mask received halothane in 14% oxygen, while those in the other mask received halothane in 12% oxygen. Metabolites were collected as described above.

### *Assessment of Hepatic Injury*

Alanine aminotransferase (ALT) activity was measured in serum prepared from blood collected at the time of killing. Liver tissue was fixed in formalin, cleared in acetone, and embedded in epoxy resin. Two-micron sections were stained with hematoxylin and eosin and examined by a pathologist (PH) who was unaware of the sex of the animal and the treatment received.

### *Measurement of Nonvolatile Metabolites*

Urinary fluoride and serum bromide concentrations were measured with ion-specific electrodes (Orion Research Inc., Cambridge, MA). Serum bromide concentrations of rats that had not received halothane were too low to be measured accurately using this technique.

### *Statistical Methods*

The results indicated that urinary fluoride excretion ( $\mu\text{mol}/22 \text{ hr}$ ) by control rats was approximately proportional to body weight. Because male and female rats differed considerably in weight, fluoride excretion was expressed as  $\mu\text{mol}/22 \text{ hr}/\text{kg}$  body weight for analysis. Urinary fluoride excretion, serum bromide concentration, and logarithm of serum ALT activity of the treatment groups were compared by the method of randomized complete blocks, replications of the experiment forming the blocks (6). Standard error bars shown on figures were calculated from the pooled within-block variances.

For analysis of CTF exhalation, area under the con-



centration  $\times$  time curve from 0–115 min (AUC) was calculated by the trapezoidal rule for each group of three rats. It was considered that the difference,  $\log(\text{AUC}_{\text{male}}) - \log(\text{AUC}_{\text{female}})$ , would more closely approximate a normal distribution than the differences calculated from the untransformed areas. This supposition was supported by data from the experiments described here as well as others carried out in our laboratory. Hence, logarithms of the AUCs of the treatment groups were compared by Student's paired *t*-tests. Exhaled amounts of CDF closely paralleled those of CTF, and so CDF exhalation was not subjected to statistical analysis.

## Results

### End-Expired Gases

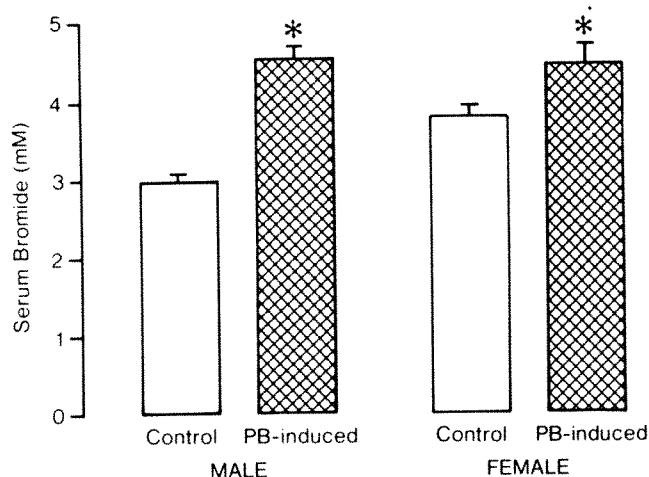
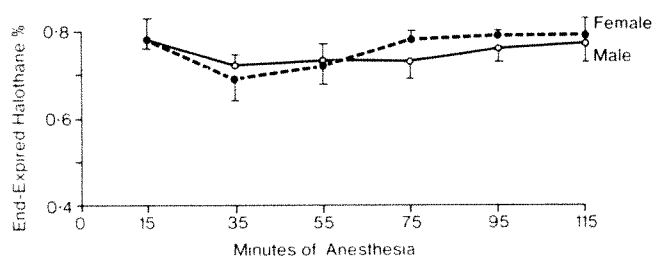
Carbon dioxide concentrations in the breath samples taken during anesthesia were approximately 80–90% as great as end-expired concentrations measured by mass spectrometry for both sexes. Thus the technique used for collection of breath samples seems to give a reasonable approximation to end-expired breath. Concentrations of halothane in the breath samples were similar for the two sexes (Fig. 1).

### Effect of PB Induction on Halothane Metabolism

PB-induced animals of both sexes had higher post-halothane serum bromide concentrations than did un-induced animals ( $P < 0.05$ ) (Fig. 2). PB induction resulted in an increase of about 1.5-fold in serum bromide concentrations of halothane-exposed male rats, but only about 1.2-fold in females.

The increase in reductive halothane metabolism brought about by PB was also greater in males than in females. CTF exhalation was increased by a factor of 2.5 (95% confidence limits, 1.6–3.9) in males, but only 1.4 (95% confidence limits, 0.6–3.3) in females. PB induction led to an increase in post-halothane

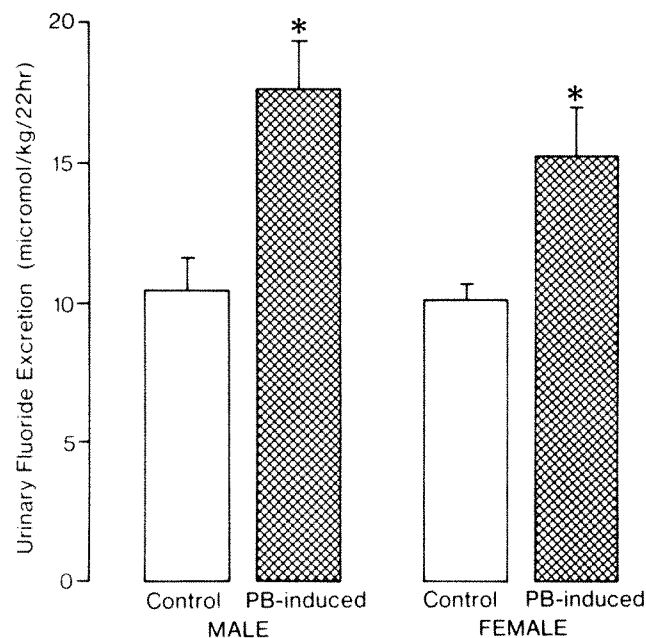
**Figure 1.** Concentration of halothane in the pooled exhaled breath of male and female rats during anesthesia. Each point is the mean  $\pm$  SEM for four groups each of three rats.



**Figure 2.** Serum bromide concentrations 24 hr after halothane anesthesia of control and PB-induced rats. PB induction resulted in increased bromide levels in both sexes. Mean  $\pm$  pooled within-experiment SEM. \* $P < 0.05$  compared to control.

fluoride excretion of  $7.2 \pm 4.4$  (mean  $\pm$  95% confidence limits)  $\mu\text{mol}\cdot\text{kg}^{-1}\cdot 22\text{ hr}^{-1}$  in male rats, and  $5.1 \pm 3.7$  in female rats (Fig. 3). The increase caused by PB induction does not differ significantly between the two sexes for both CTF and fluoride excretion ( $P > 0.05$  in each case). However, these experiments were designed to establish the effect of PB induction within

**Figure 3.** Urinary fluoride excretion in the 22-hr period after halothane anesthesia. PB induction led to increased fluoride excretion in both sexes. Mean  $\pm$  pooled within-experiment SEM. \* $P < 0.05$  compared to control.

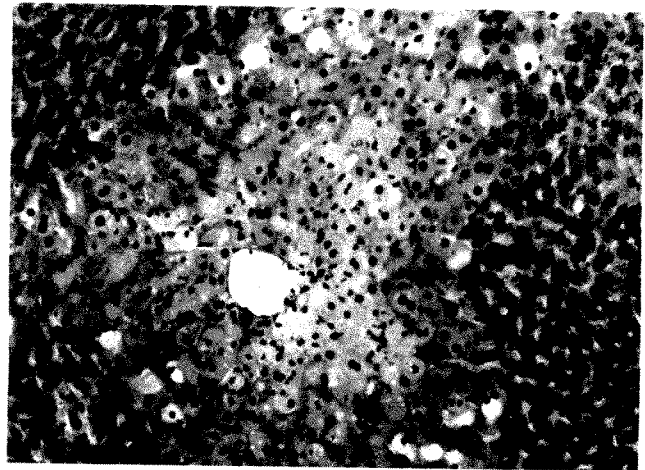
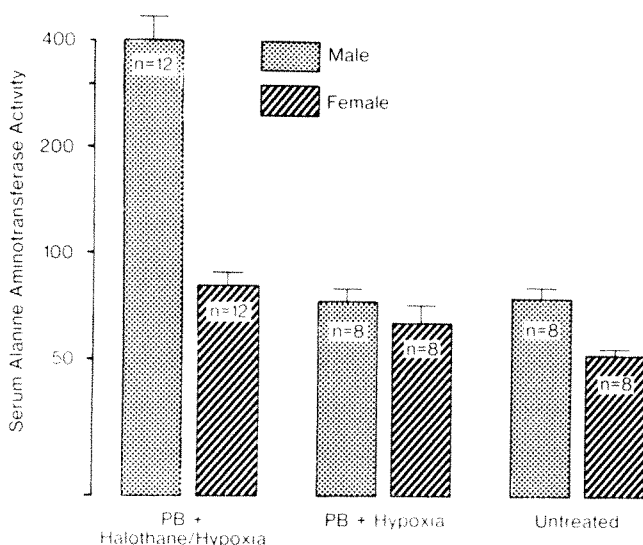


each sex, and provide little power for between-sex comparisons that were based on experiments involving concurrent anesthesia of both sexes to eliminate among-experiment variation.

### Sex Difference in Halothane Hepatotoxicity

Consistent with earlier reports, serum ALT activity of male rats was not increased significantly by PB induction plus hypoxia, but the addition of halothane anesthesia to this combination led to a marked increase ( $P < 0.05$ ) (Fig. 4). ALT activities of female rats that received PB induction plus halothane-hypoxia were only slightly, but significantly, elevated compared to untreated females ( $P < 0.05$ ), but were not significantly higher than those of female rats that received PB induction plus hypoxia (Tukey's HSD test). Untreated male rats had higher serum ALT activities than untreated females. This is consistent with observations made over a number of years in our colony of Fischer 344 rats. Other workers have also reported higher ALT activity in male rats, e.g., albino Wistars (7), but the difference is usually smaller than that described here. Because of this sex difference in control rats, the sex difference in the PB induction plus halothane-hypoxia groups was assessed by comparing the sex difference in ALT activities in the PB induction plus hypoxia groups with that in the PB induction plus halothane-hypoxia groups (i.e., the interaction between these two treatments and sex). The ALT increase due to halothane was significantly ( $P < 0.01$ ) greater in males than in females.

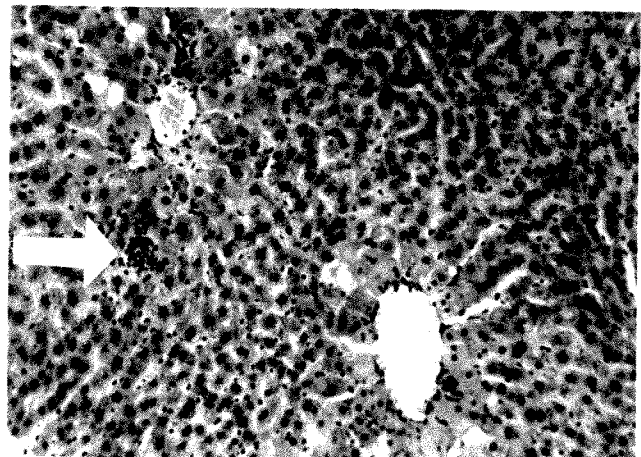
**Figure 4.** Serum ALT activity 24 hr after halothane anesthesia. Only male rats induced with PB and given halothane-hypoxia had elevated ALT activity ( $P < 0.01$ ). Mean  $\pm$  pooled within-experiment SEM.

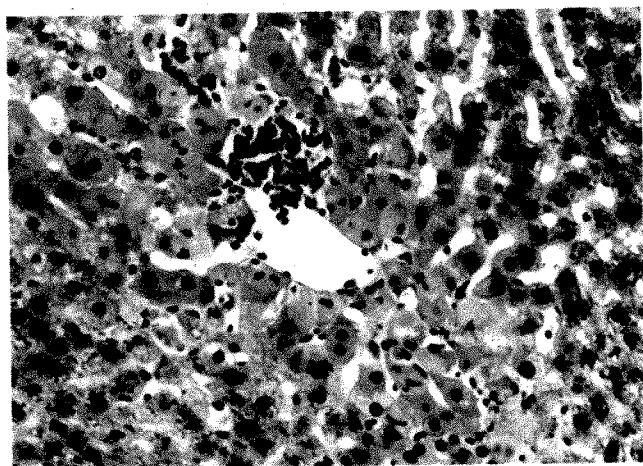


**Figure 5.** Section of liver from a male rat that received PB induction plus halothane-hypoxia, killed 24 hr after anesthesia. Confluent hepatocellular necrosis extends for a considerable distance around the central vein. H & E  $\times$  125.

Livers from control rats (untreated or PB induction plus hypoxia) of both sexes showed no sign of injury. All livers from male rats that received PB induction plus halothane-hypoxia showed confluent necrosis around the central veins, extending out toward the portal tracts (Zone 3) (Fig. 5). This type of injury was present in all 12 of the male rats that received this treatment. In contrast, of the 12 females that received PB induction plus halothane-hypoxia, the livers of four could not be distinguished from controls. The remaining eight showed injury ranging from focal necrosis (Fig. 6) to confluent centrilobular necrosis (Fig. 7). In those females with centrilobular necrosis, the lesion was less extensive than in the males, being

**Figure 6.** Section of liver from a female rat that received PB induction plus halothane-hypoxia, killed 24 hr after anesthesia. A focus of necrosis is indicated by the arrow. H & E  $\times$  125.





**Figure 7.** Section of liver from a female rat that received PB induction plus halothane-hypoxia, killed 24 hr after anesthesia. This animal had the most severe hepatic injury of all the female rats in the study. Confluent necrosis is present around the central vein. H & E  $\times 210$ .

limited to within a few cells of the central veins. Although serum ALT activities of the female rats were only slightly elevated, ALT activity was strongly associated with severity of hepatic injury (Fig. 8).

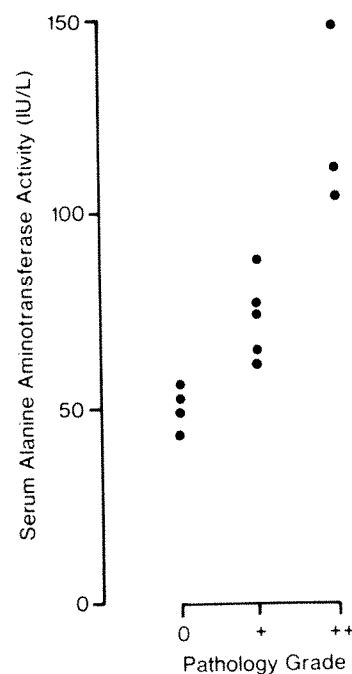
#### *Sex Difference in Halothane Metabolism*

Serum bromide concentrations were used as an index of the extent of oxidative metabolism of halothane. In rats that did not receive halothane, serum bromide concentrations were too low to measure accurately with the technique used, but were all below 1 mM. After halothane anesthesia, serum bromide concentrations of PB-induced animals were elevated in both sexes (Fig. 9). The elevation was higher in females than in males, but this difference was not statistically significant ( $0.1 > P > 0.05$ ).

In contrast, reductive metabolism of halothane was substantially greater in PB-induced males than in females. Using CTF exhalation as an index, reductive metabolism was 3.1-fold (95% confidence limits, 2.2 to 4.5) greater in males (Table 1). The increase in urinary fluoride excretion that followed halothane anesthesia of PB-induced animals was also greater in males ( $P < 0.05$ ), though the difference in this case was a factor of only about 1.5 (allowance being made for the level of fluoride excretion by control rats) (Fig. 10).

#### *Effect of Decreasing Inspired Oxygen Concentration*

Anesthesia of female rats in 12% oxygen instead of 14% oxygen resulted in increased excretion of reduced metabolites. CTF exhalation in the 12% oxygen group



**Figure 8.** Serum ALT activities of female rats 24 hr after PB induction plus halothane-hypoxia. Though ALT activities were not greatly elevated, there was a strong association between ALT and severity of hepatic injury. (Symbols: 0, no injury; +, focal necrosis; ++, confluent necrosis.)

was 843 ppm·min (AUC 0–115 min) compared to 411 in the 14% oxygen group. Post-halothane urinary fluoride excretion was also higher in the 12% oxygen group ( $16.9 \pm 1.0$  vs  $11.9 \pm 1.9 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ , mean  $\pm$  SEM,  $n = 5$ ,  $P < 0.05$ ). Although these increases indicated that extent of reductive halothane metabolism had been brought nearer to that observed

**Figure 9.** Comparison of serum bromide levels in male and female rats 24 hr after halothane anesthesia. Bromide concentrations did not differ significantly ( $P > 0.05$ ) between the two sexes. Mean  $\pm$  pooled within-experiment SEM.

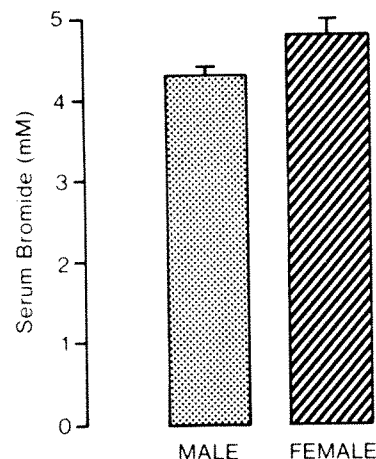




Table 1. CTF Exhalation during Halothane Anesthesia

	Females	Males	Male:Female ratio
Experiment 1	820*	1950	2.38
Experiment 2	750	2210	2.95
Experiment 3	290	1200	4.14
Experiment 4	240	780	3.25

\*Area under concentration  $\times$  time curve from 0-115 min, in ppm-min.

in PB-induced male rats anesthetized in 14% oxygen, none of the female rats had confluent hepatocellular necrosis. Livers of all ten showed only focal necrosis, which was not discernibly more severe in the 12% oxygen group.

## Discussion

The results presented here confirm the report by Jee et al. (2) that female rats are less susceptible to halothane hepatotoxicity than males. Jee et al. reported only minimal cellular disruption, and no increase in serum ALT, after hypoxic halothane anesthesia of PB-induced female rats. In our studies, a range of responses, from no injury to centrilobular necrosis, which was limited to within a few cells of the central vein, was observed in female rats under these conditions. The extent of hepatic injury, when it occurred, was always much less than in males, and serum ALT activities were only slightly elevated. The animals used

in our study were Fischer 344 rats, while Jee et al. used Sprague-Dawley rats. It has been shown that male Fischer 344 rats are more susceptible to halothane hepatotoxicity than are male Sprague-Dawley rats (8). No direct comparison has been made involving female rats; however, such a strain difference might explain the seemingly more severe injury in some of our female rats than reported by Jee et al.

Under conditions resulting in halothane hepatotoxicity, the extent of reductive metabolism of halothane was less in female rats than in males. Although we did not identify a statistically significant difference in the effect of PB induction on reductive metabolism, our results suggest that such a difference may exist. It appears likely that the greater amount of reductive metabolism in PB-induced males compared to females is due to both a higher level prior to induction, and a greater increase after PB induction.

It is possible that the substantial difference in weight of the male and female rats used in this study contributed to the observed differences in halothane metabolism and hepatotoxicity. Female rats are in general lighter than male rats of similar age; we felt it appropriate to use animals of similar age and accept the weight difference as part of the inherent difference between the sexes. Other studies in our laboratory have, however, shown that young male rats, lighter than the females used in this study, metabolize halothane in a similar manner to adult males and show similar post-halothane serum enzyme elevations (unpublished data). It thus seems unlikely that differences in body weight of the two sexes were an important influence in the present study.

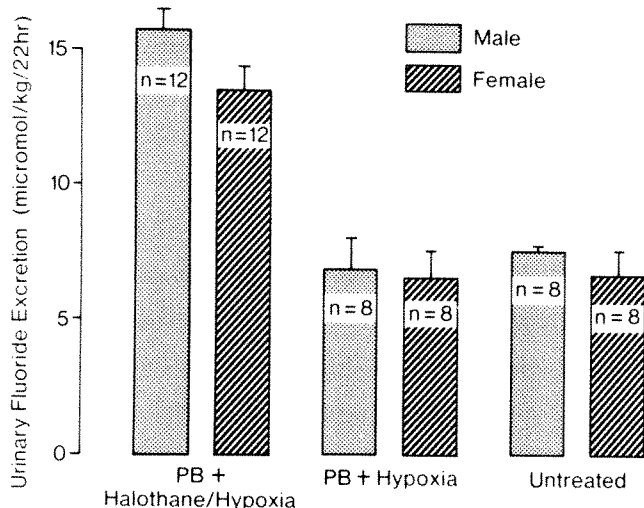
The sex difference in reductive metabolism appears, however, not to be the major factor in the difference in hepatic response. By reducing the inspired oxygen concentration to 12%, we were able to increase the extent of reductive metabolism in females by about twofold, so that it approached the level typically seen in males. This procedure, however, did not result in more severe hepatic injury. Further factors must therefore be involved in the sex difference in halothane hepatotoxicity in rats.

The authors are grateful to the Department of Clinical Biochemistry, Flinders Medical Centre, for assistance in the measurement of serum alanine aminotransferase activity.

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Figure 10. Urinary fluoride excretion after halothane anesthesia and in control rats. Fluoride excretion did not differ significantly between the sexes when halothane had not been administered. The increase in fluoride excretion after halothane anesthesia was greater in males than in females ( $P < 0.05$ ). Mean  $\pm$  pooled within-experiment SEM.



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## Regional Coronary Hemodynamics during Isoflurane–Nitrous Oxide Anesthesia in Patients with Ischemic Heart Disease

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REIZ S, ÖSTMAN M. Regional coronary hemodynamics during isoflurane–nitrous oxide anesthesia in patients with ischemic heart disease. *Anesth Analg* 1985;64:570–6.

*The effects of 1.5 MAC isoflurane–nitrous oxide anesthesia on central hemodynamics, regional coronary blood flow, myocardial oxygenation, and lactate balance were investigated in 13 patients with coronary artery disease. Mean arterial pressure was reduced 45% mainly because of systemic vasodilation. Great cardiac venous flow (GCVF) decreased, whereas total coronary sinus blood flow (CSF) was unchanged. Total coronary resistance and resistance in the area drained by the GCVF decreased as did myocardial oxygen extraction, demonstrating coronary vasodilation. The GCVF/CSF ratio did not decrease despite the reduction in resistance to left ventricular ejection. Seven patients had*

*ECG and metabolic indications of myocardial ischemia (lactate extraction reduced from  $22 \pm 5\%$  to  $7 \pm 3\%$ ,  $P < 0.02$  for the group). Changes in GCVF and oxygen consumption in the corresponding area correlated closely ( $r = 0.943$ ). However, the regression line was shifted to the left and three patients, who became ischemic, had an increase in GCVF despite unchanged or decreased myocardial oxygen demand. It is concluded that isoflurane may cause coronary blood flow redistribution with regional myocardial ischemia in patients with coronary artery disease.*

**Key Words:** ANESTHETICS, VOLATILE—isoﬂurane. HEART, CORONARY BLOOD FLOW—myocardial oxygenation.

Isoflurane produces a dose-dependent reduction in cardiac contractility (1). The agent is a potent systemic vasodilator, and in healthy subjects cardiac output is well preserved by an increase in heart rate (2,3). Patients with ischemic heart disease frequently have impaired baroreceptor function and may suffer substantial reduction in blood pressure during isoflurane anesthesia (4–6). As expected with agents that reduce afterload and cardiac contractility, isoflurane decreases myocardial oxygen demand (6,7). Studies of the effects of isoflurane on the canine coronary circulation have demonstrated that isoflurane is a potent coronary vasodilator (8,9). Similar effects have been documented in patients with coronary artery disease (6). Isoflurane is indeed a more potent coronary vasodilator than halothane and enflurane (10,11). Our group has previously demonstrated that 1 MAC isoflurane anesthesia may be associated with a high incidence of regional myocardial ischemia when used in patients with coronary artery disease (6). We sug-

gested that hypotension and redistribution of coronary blood flow ("coronary steal") due to the direct coronary vasodilatory action of isoflurane were the two mechanisms producing myocardial hypoxia in patients with ischemic heart disease. We have also demonstrated that nitrous oxide augments the coronary vasodilating property of enflurane and isoflurane, both when added to (increased MAC) or when partly exchanged for (unchanged MAC) the basal anesthetic agent (11,12).

The aim of the present study was to investigate whether isoflurane–nitrous oxide might produce redistribution of coronary blood flow in patients with ischemic heart disease. For this purpose, the retrograde, multiple thermistor coronary blood flow thermodilution technique described by Pepine et al. (13) was used. This method permits simultaneous determinations of great cardiac venous flow and total coronary sinus blood flow.

### Material and Methods

Thirteen patients scheduled for surgery on the abdominal aorta or the common iliac arteries were studied after we obtained their informed consent. The study was approved by the Ethics Committee of the University of Umeå. All patients suffered from isch-

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Table 1. Clinical Patient Data

Patient number	Age	Sex	Angina	Previous MI	Hypertension	History of CHF	NYHA class	Medication(s)
1	58	M	+	—	—	—	I	Nitroglycerin
2	53	M	+	+	—	+	III	Atenolol 0.1 g $\times$ 1
3	55	M	+	+	—	+	III	Metoprolol 0.1 g $\times$ 2, nitroglycerin
4	68	M	+	+	—	—	II	Nitroglycerin
5	71	M	+	—	+	—	I	Chlorothalidon 50 mg $\times$ 1
6	64	M	+	+	—	+	III	Digoxin 0.25 mg $\times$ 1, furosemid 80 + 40 mg
7	54	M	+	—	—	—	I	Nil
8	67	F	+	—	—	—	II	Nitroglycerin
9	69	M	+	—	+	+	III	Hydrochlorothiazid 25 mg $\times$ 1, quinidin 400 mg $\times$ 2, terbutalin 7.5 mg $\times$ 1, theophyllin 200 mg $\times$ 1
10	58	M	+	—	+	+	III	Digoxin 0.25 mg $\times$ 1, apresolin 25 mg $\times$ 3
11	56	M	+	—	—	+	II	Nitroglycerin
12	68	M	+	—	+	+	I	Hydrochlorothiazid 50 mg $\times$ 1, amilorid chlorid 5 mg $\times$ 1
13	59	M	+	—	+	—	II	Bendroflumethiazid 2.5 mg $\times$ 1, nitroglycerin

Abbreviations: MI, myocardial infarction; CHF, congestive heart failure.

emic heart disease diagnosed by a history of angina pectoris, previous myocardial infarction(s), and either coronary angiograms or positive bicycle ergometer tests. Relevant patient data are outlined in Table 1.

The unpremedicated patients were brought to the operating room where, when they were under local anesthesia, brachial or radial arterial catheters were inserted together with a pulmonary artery thermodilution catheter and a Pepine regional coronary sinus catheter. The latter was carefully placed under fluoroscopy with its distal mixing thermistor in the great cardiac vein and its proximal mixing thermistor in the common coronary sinus approximately 2 cm from the coronary sinus ostium. With this position, admixture of blood from the right atrium is unlikely to occur at the level of the proximal thermistor as long as right atrial pressure is not markedly elevated (14,15). The position of the coronary sinus catheter was regularly rechecked with dye injections during the course of the investigation to ensure stable position. The ECG (lead V<sub>5</sub>) and arterial, pulmonary arterial, and right atrial pressures were recorded continuously throughout the study on a Mingograf 82 recorder via Siemens-Elema's pressure transducers 746/51 positioned at midchest. Water standards at 0 and 68 cm water (50 mm Hg) were used. Cardiac output was determined in triplicate by thermodilution using 5 ml of ice-cold normal saline for each mechanically driven injection, synchronized to end expiration during either spontaneous or mechanical ventilation. Great cardiac venous flow and total coronary sinus blood flow were determined by the retrograde thermodilution technique originally described by Ganz et al. (16) and modified for regional blood flow measurement by Pe-

pine et al. (13). Normal saline at room temperature was used as the indicator and injected at 40 ml/min over approximately 20 sec for each measurement. The coronary sinus catheter has one hole only, used for both indicator injection and blood sampling. Accordingly, the blood withdrawn via the catheter represents left anterior descending artery perfusion, which is drained by the great cardiac vein.

Anesthesia was induced with isoflurane-nitrous oxide-oxygen delivered by face mask. Fifty mg of thiopental was injected rapidly to avoid excitation with tracheal intubation performed after administering 1.5 mg/kg of succinylcholine. The tracheal tube was connected to an Engström ECS 2000 volume cycled ventilator, and muscle relaxation was produced with 0.1 mg/kg of pancuronium bromide. Ventilation was adjusted to give an arterial carbon dioxide tension comparable to the awake level. The inspired nitrous oxide concentration was kept at 70%. Isoflurane was then adjusted by a mass-spectrometer calibrated Engström EMMA with a water vapor filter incorporated in the anesthetic circuit to produce an anesthetic level of 1.5 MAC.

Measurements of pressures, blood flows, myocardial oxygen consumption and extraction, and myocardial lactate extraction were performed before induction of anesthesia and immediately before surgery—approximately 45 min after induction of anesthesia. Measurement techniques and derivation of all variables have been described previously in detail (6). A list of abbreviations used in text and figures is given in Table 2.

The Wilcoxon test for paired observations and conventional regression analysis was used for the statis-

Table 2. List of Abbreviations Used in Text and Figures

MAP	Mean arterial pressure (mm Hg)
PCW	Pulmonary capillary wedge pressure (mm Hg)
RAP	Right atrial pressure (mm Hg)
CPP	Coronary perfusion pressure—diastolic arterial pressure minus PCW (mm Hg)
HR	Heart rate (beats/min)
CI	Cardiac index ( $L \cdot min^{-1} \cdot m^{-2}$ BSA)
SVI	Stroke volume index ( $ml/m^2$ )
SVR	Systemic vascular resistance ( $mm\ Hg \cdot L^{-1} \cdot min^{-1} \cdot m^2$ )
PVR	Pulmonary vascular resistance ( $mm\ Hg \cdot L^{-1} \cdot min^{-1} \cdot m^2$ )
CSF	Coronary sinus blood flow (ml/min)
GCVF	Great cardiac venous blood flow (ml/min)
$M\dot{V}O_2$	Oxygen consumption in the area drained by the great cardiac vein (ml/min)
$Mo_2$ extr.	Oxygen extraction in the area drained by the great cardiac vein (%)
Myoc. lact. extr.	Lactate extraction in the area drained by the great cardiac vein (%)
CVR	Total coronary vascular resistance ( $mm\ Hg \cdot L^{-1} \cdot min^{-1}$ )
LVCVR	Coronary vascular resistance in the area drained by the great cardiac vein ( $mm\ Hg \cdot L^{-1} \cdot min^{-1}$ )
LAD	Left anterior descending artery
CAD	Coronary artery disease

tical analyses of the data. A *P* value less than 0.05 was considered statistically significant. All results are presented as mean  $\pm$  SEM.

## Results

One and one half MAC isoflurane–nitrous oxide anesthesia significantly decreased MAP ( $-45\%$ ,  $P < 0.01$ ), CI ( $-17\%$ ,  $P < 0.01$ ), and SVR ( $-40\%$ ,  $P < 0.1$ ). HR, PCW, RAP, SVI, and PVR were not significantly altered (Fig. 1). CPP decreased ( $-45\%$ ), CSF remained unchanged, and GCVF decreased ( $-25\%$ ,  $P < 0.01$ ). CVR and LVCVR were both reduced ( $-40\%$ ,  $P < 0.01$  and  $-22\%$ ,  $P < 0.05$ , respectively),  $M\dot{V}O_2$  decreased ( $-45\%$ ,  $P < 0.01$ ) as did  $Mo_2$  extraction ( $-23\%$ ,  $P < 0.01$ ) (Fig. 2). There was a close correlation between the reductions in GCVF and  $M\dot{V}O_2$  ( $r = 0.943$ ,  $P < 0.001$ ) (Fig. 3). Before anesthesia, the GCVF/CSF ratio ranged from 0.45 to 0.71 in 12 of the patients and was 0.34 in the remaining patient. With anesthesia, the GCVF/CSF ratio remained unchanged (two patients) or increased (two patients) in four and decreased in nine patients (Fig. 2). Some  $V_5$  ST–T changes suggestive of myocardial ischemia were recorded in seven of the patients. Lactate extraction in the area drained by the great cardiac vein decreased significantly in

these seven patients ( $-68\%$ ,  $P < 0.02$ ). Lactate production occurred in one of the seven patients (Fig. 2). In the six remaining patients who did not develop ST–T changes with induction of anesthesia, there was no reduction in myocardial lactate extraction. The  $V_5$  ECG in relation to myocardial lactate extraction is outlined for the individual patients in Table 3. The ECG changes reverted to awake patterns with commencement of surgery in four patients in whom isoflurane was continued, and in one patient after discontinuation of isoflurane. In two patients, the ECG abnormality persisted throughout the operation despite normal blood pressure. One of these patients, who had never been hypotensive, hypertensive, or tachycardic during anesthesia and surgery (patient 5, Table 1) developed ECG and enzyme evidence of an acute myocardial infarction on the third postoperative day, from which he subsequently died. None of the other patients with ischemic ECG changes during anesthesia had ECG or enzyme evidence of myocardial infarction during the postoperative course.

## Discussion

The effects of isoflurane–nitrous oxide anesthesia on the systemic circulation in the present study are consistent with those reported earlier by us and by others in patients with coronary artery disease (6,12,17). Mean arterial pressure decreased by 45%, mainly due to systemic vasodilation (SVR,  $-45\%$ ) (Fig. 1). Consistent with previous findings by Hess et al. (18), patients with elevated PCW before anesthesia demonstrated marked reductions in PCW during anesthesia; but in the group as a whole, PCW was unchanged and cardiac output decreased slightly ( $-17\%$ ), suggesting moderate cardiodepression. Heart rate did not change as previously reported in comparable patients anesthetized with isoflurane–nitrous oxide (12).

As expected from the decrease in resistance to left ventricular ejection and reduction in cardiac contractility with isoflurane–nitrous oxide anesthesia, myocardial oxygen consumption decreased in the area perfused by the left anterior descending artery (LAD) and drained by the great cardiac vein (GCV). This was accomplished by reductions in both great cardiac venous blood flow (GCVF) and myocardial oxygen extraction. In humans, the LAD normally perfuses 50–70% of the left ventricular mass under resting conditions (19). Our findings of GCVF/CSF ratios between 0.45 and 0.71 before anesthesia in 12 of our patients demonstrate that the regional blood flow measurement method gives adequate values for the distribution of coronary blood flow. For the group,

Table 3. The V<sub>5</sub> ECG and Anterior Wall Lactate Extraction before and during Isoflurane-Nitrous Oxide Anesthesia in the Individual Patients

Patient number	ECG at rest	Lact. extr. at rest (%)	ECG during anesthesia	Lact. extr. during anesthesia (%)	Duration of ECG changes, comments
1	N	30	↓	13	ECG normal 10 min after commencement of surgery. Normal postop enzymes.
2	↓ + Neg T	10	Unchanged	9	—
3	N	22	N	8	—
4	↓	38	↓↓	13	Persist throughout operation, normal postop enzymes day 1-3.
5	(↓)	2	↓↓	1	Persist throughout operation, postop enzymes normal day 1,2, develops fatal MI postop day 3.
6	N	15	Flat T-wave	13	—
7	N	21	↓	6	18 min, disappear with discontinuation of isoflurane-nitrous oxide anesthesia. Normal postop enzymes.
8	N	32	↑	16	ECG normal 12 min after commencement of surgery. Normal postop enzymes.
9	N	18	↓	3	ECG normal 8 min after commencement of surgery. Normal postop enzymes.
10	↓ Bigeminal PVC-s	-3	Unchanged disappearance of PVCs	0	—
11	N	11	N	18	—
12	↓	14	Unchanged	22	—
13	N	13	↓↓	-6	ECG normal 15 min after commencement of surgery. Normal postop enzymes.

Abbreviations: N, normal; ST-depression, (↓) 0-1 mm, ↓ 1-2 mm, ↓↓ 2-3 mm; ST-elevation, ↑ 1-2 mm; PVC, premature ventricular contraction.

total coronary sinus blood flow (CSF) did not decrease with anesthesia despite the marked reduction in coronary perfusion pressure. In some patients, CSF even increased (Fig. 2). GCVF decreased, but less than perfusion pressure, demonstrating general but nonuniform coronary vasodilation. Accordingly, the GCVF/CSF ratio was markedly and unpredictably altered by isoflurane-nitrous oxide anesthesia (Fig. 2). With normal coronary autoregulation, a marked decrease in resistance to left ventricular ejection without change in right ventricular afterload or heart rate after anesthesia would cause the GCVF/CSF ratio to decrease. Nevertheless, this ratio increased or remained unaltered in four of the 13 patients, demonstrating an absolute or relative increase in blood flow in the LAD area despite a reduction in myocardial oxygen demand.

During 1.5 MAC isoflurane-nitrous oxide anesthesia, seven of our 13 patients developed V<sub>5</sub> ST-T changes on their electrocardiogram, which suggests anterior wall ischemia. One of these patients developed myocardial lactate production and, for the group of patients with ECG signs of ischemia, myocardial lactate extraction decreased markedly ( $22 \pm 5\%$  to  $7 \pm 3\%$ ,  $P < 0.02$ ). In the remaining six patients with unchanged V<sub>5</sub> ECG ST-T segments, there was no significant alteration in myocardial lactate extraction (Fig.

2, Table 3). In this group, one patient with lactate production and high wedge pressure before anesthesia improved metabolically without ECG changes when his high coronary back pressure was reduced by the anesthetics. In only two patients (numbers 1 and 4) were the ECG changes associated with increase in heart rate parallel to the reduction in coronary perfusion pressure (HR 53 to 70 and 88 to 99 beats/min, respectively, with MAP 110 to 80 and 110 to 60 mm Hg, respectively). In the latter, the ECG changes persisted throughout surgery with MAP approximately 100 mm Hg and HR approximately 100 beats/min (Fig. 1).

Interpretation of myocardial lactate extraction data for the diagnosis of regional myocardial ischemia is controversial. During hypotension, blood flow through a critical coronary artery stenosis may be reduced so that lactate is hardly released to the coronary sinus. Similarly, lactate produced during ischemia in one area of the myocardium during a hypermetabolic state, i.e., during hypertension and tachycardia, may be diluted by blood from nonischemic areas. Consequently, myocardial lactate extraction is not necessarily reduced during regional ischemia and anesthesia. In the present study, we found a highly significant reduction in lactate extraction from a mean of 22 to 7% in the area drained by the great cardiac



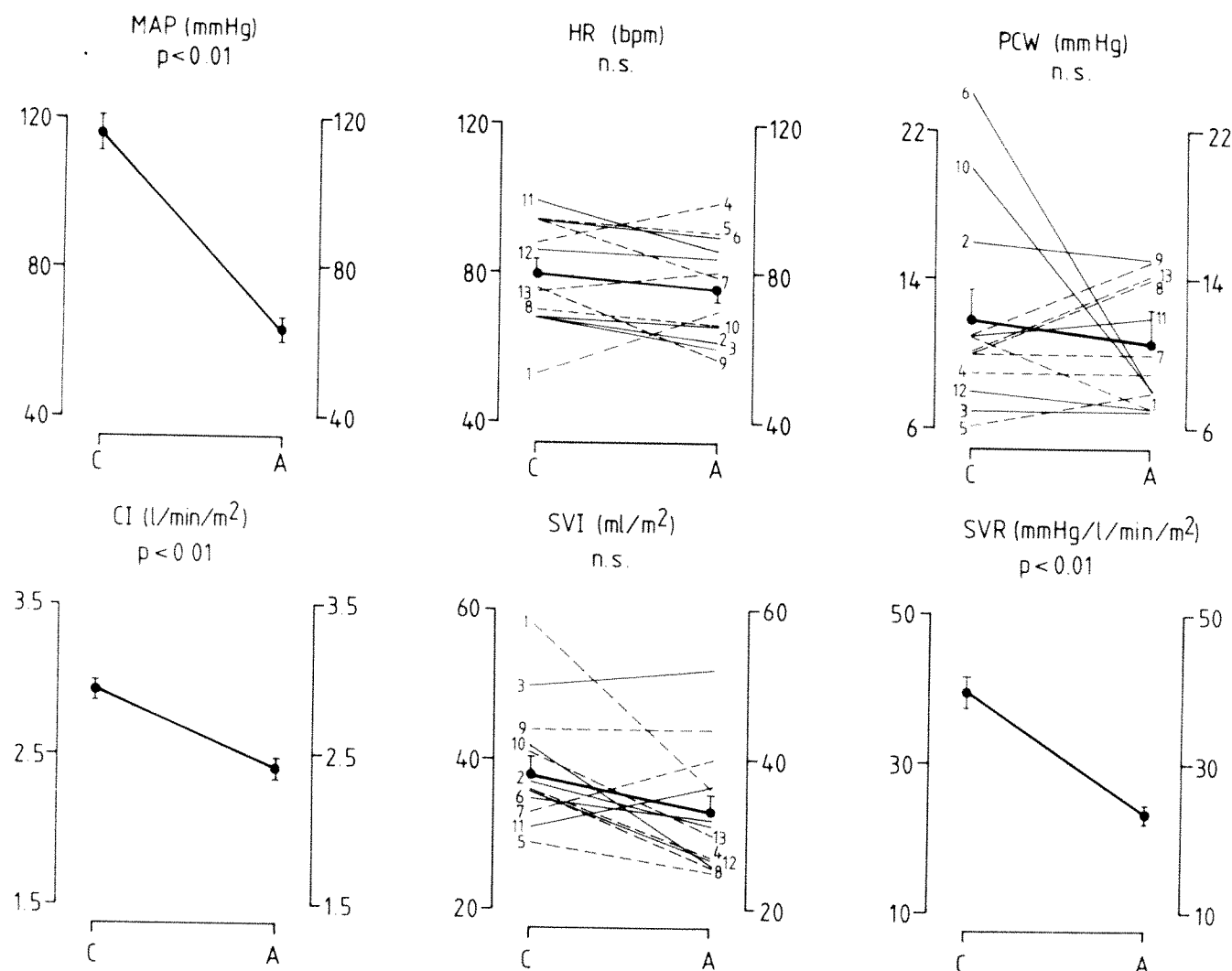


Figure 1. Hemodynamic effects of 1.5 MAC isoflurane-nitrous oxide anesthesia (A). Note the marked reduction in PCW from control (C) in the two patients with supranormal filling pressures after reduction in resistance to left ventricular ejection. Patients who developed ECG changes suggestive of ischemia are denoted with dashed lines. Patients are numbered as in Table 1. For abbreviations see Table 2.

vein parallel to the development of  $V_5$  ECG changes suggestive of ischemia. In comparison, the group of patients in whom ECG changes were not observed did not present any change in anterior wall lactate extraction. The GCVF/CSF ratio increased or remained unaltered in four of the seven patients with ECG and metabolic changes suggesting ischemia. Myocardial oxygen extraction decreased in all patients. Our findings, therefore, demonstrate that the coronary vasodilation and the redistribution of blood flow were not due to a metabolic response to inadequate myocardial oxygenation only. The decrease in oxygen consumption in the area supplied by the LAD correlated highly with the reduction in GCVF ( $r = 0.943$ ). However, in three of the patients, all of whom developed ECG evidence of myocardial ischemia, isoflurane-nitrous oxide anesthesia decreased myocardial oxygen consumption by 3 to 25%, parallel to an increase in GCVF by 16 to 28%. Consequently,

isoflurane-nitrous oxide anesthesia was associated with a leftward shift of the coronary blood flow/myocardial oxygen consumption relationship with a coronary vasodilation overriding normal coronary autoregulation (Fig. 3).

In conclusion, we have demonstrated that isoflurane-nitrous oxide administered to patients with ischemic heart disease may produce substantial and unpredictable redistribution of coronary blood flow with increase in regional blood flow, despite a reduction in myocardial oxygen demand in the very same area of the myocardium. Regional myocardial ischemia may

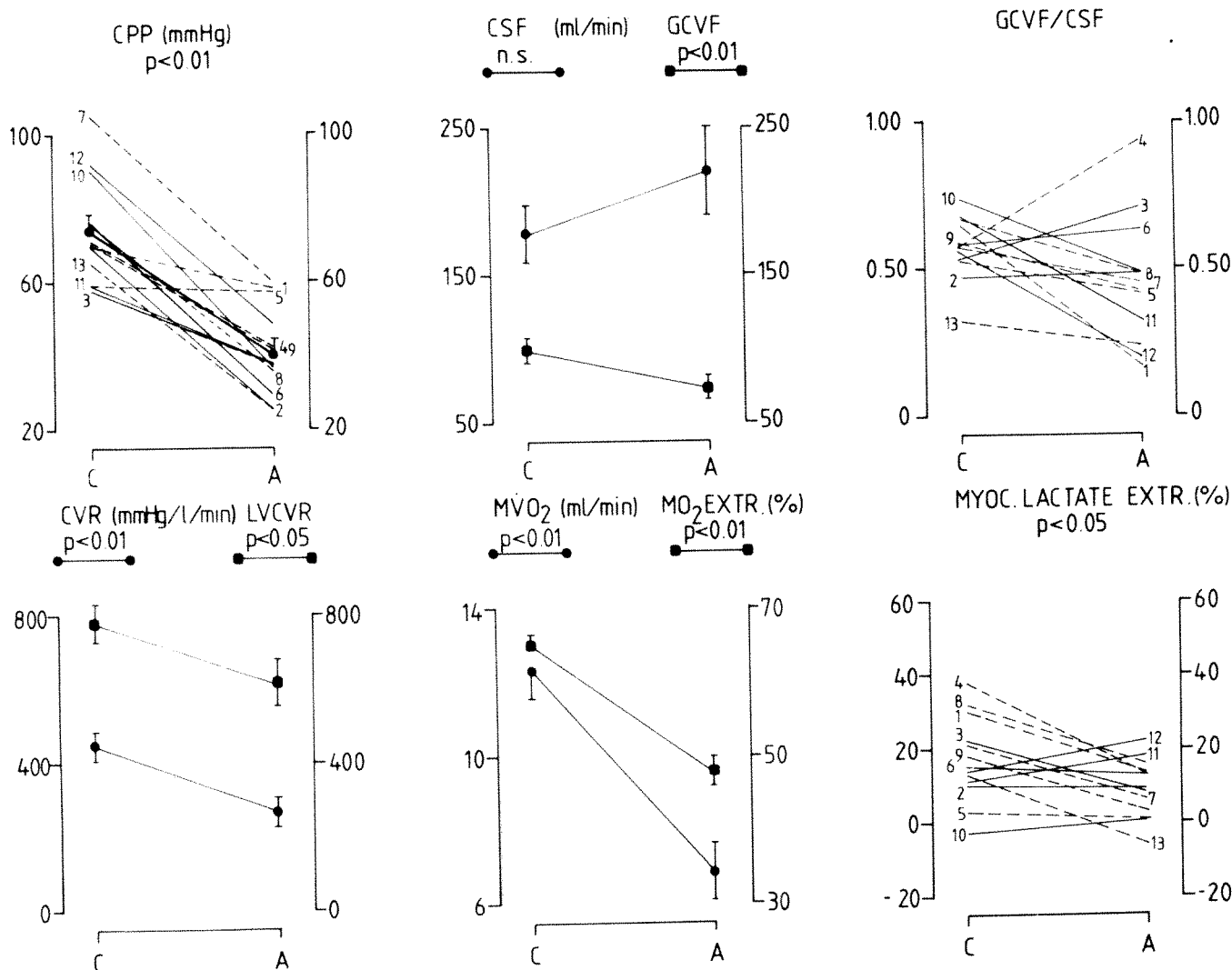
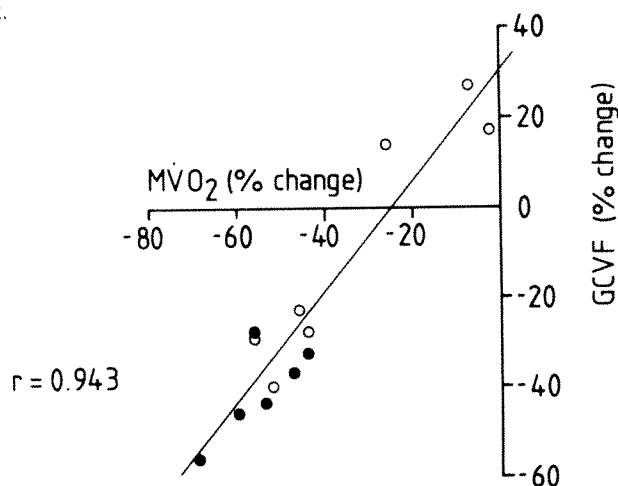


Figure 2. Effects of 1.5 MAC isoflurane-nitrous oxide anesthesia on regional coronary hemodynamics, myocardial oxygenation, and myocardial lactate balance (A). Note the unexpected increase in GCVF/CSF ratio from control (C) in one of the patients showing myocardial ischemia (dashed lines). There was no difference in reduction in coronary perfusion pressure (CPP) between patients who did or did not develop myocardial ischemia. Patients are numbered as in Table 1. For abbreviations see Table 2.

Figure 3. Relationship between changes in myocardial oxygen consumption ( $\dot{M}V O_2$ ) in the area drained by the great cardiac vein and great cardiac venous blood flow (GCVF). Three patients, who all became ischemic during anesthesia (open circles), increased GCVF despite unchanged or reduced myocardial oxygen demand. Note the leftward shift of the regression line demonstrating interference with normal coronary autoregulation. For abbreviations see Table 2.



result. However, it is impossible to differentiate between hypotension and coronary blood flow redistribution ("coronary steal") as the dominant mechanism. In patients with markedly decreased coronary vascular reserve behind a critical stenosis, a coronary vasodilating anesthetic may cause maximal poststenotic vasodilation, thereby making perfusion of this area of the myocardium totally pressure dependent. Under such conditions, patients will tolerate only minor reduction in coronary perfusion pressure despite decreased myocardial oxygen demand. Consequently, if isoflurane-nitrous oxide anesthesia is to

be used in patients with ischemic heart disease, we recommend that blood pressure and left ventricular filling pressure be kept close to normal to avoid at least one cause of myocardial ischemia.

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## Influence of Fentanyl and Morphine on Intestinal Circulation

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*The influence of fentanyl and morphine on the intestinal circulation was evaluated in an isolated loop preparation in 37 dogs anesthetized with pentobarbital intravenously. Selected intestinal segments were pumped with aortic blood at a constant pressure of 100 mm Hg. A mixture of  $^{86}\text{Rb}$  and 9- $\mu\text{m}$  spheres labeled with  $^{141}\text{Ce}$  was injected into the arterial cannula supplying the intestinal loop, while mesenteric venous blood was collected for activity counting. A strong correlation was found between the clearances of rubidium and microspheres ( $r = 0.97$ ,  $P < 0.0001$ ), suggesting that the shunting of 9- $\mu\text{m}$  spheres through the intestines reflects the shunting of blood through nonnutritive vessels. Intravenous fentanyl decreased oxygen uptake ( $\text{O}_2\text{up}$ ), and vascular resistance (VR), and increased blood flow (BF), rubidium and microsphere clearances (Cl-Rb, Cl-Sph, re-*

*spectively), and permeability-surface area product (PS) in a dose-related fashion. Intravenous morphine in a dose of 1  $\text{mg}\cdot\text{kg}^{-1}$  increased Cl-Rb (nutritive BF) without changes in total (nutritive and nonnutritive) BF. This increase in nutritive BF is probably related to morphine-induced histamine release. Morphine in a dose of 5  $\text{mg}\cdot\text{kg}^{-1}$  was accompanied by vasoconstriction that was completely abolished by  $\alpha$ -adrenoceptor blockade. The data suggest that morphine-induced intestinal vasoconstriction is mediated via a release of epinephrine, apparently from the adrenal medulla. It is concluded that changes in the intestinal circulation during anesthesia with narcotics might play a certain role in the cardiovascular homeostasis during anesthesia and surgery. An increase in oxygen content in portal venous blood, resulting from a decrease in intestinal oxygen uptake, should facilitate hepatic oxygenation.*

**Key Words:** ANALGESICS—fentanyl, morphine.  
GASTROINTESTINAL TRACT—blood flow.

Anesthesia with fentanyl or morphine is characterized by stable cardiac output and systemic arterial pressure (1,2). Stability of the systemic circulation can be maintained by certain compensatory changes in regional circulation; for example, the splanchnic circulation plays an important role in the maintenance of homeostasis during anesthesia (3,4). It has been shown in humans that morphine,  $0.2 \text{ mg}\cdot\text{kg}^{-1}$ , increases splanchnic blood flow by 19% (5). Somewhat similar results have also been found in monkeys: morphine,  $2 \text{ mg}\cdot\text{kg}^{-1}$ , decreased blood pressure slightly, had no effect on cardiac output, and increased portal blood flow by 23% (6). However, in dogs, doses of  $1 \text{ mg}\cdot\text{kg}^{-1}$  morphine significantly increased blood flow (by 50%), while doses of  $3 \text{ mg}\cdot\text{kg}^{-1}$  decreased blood flow (by 40%) in the cranial mesenteric artery (7). These data show that the mechanisms of morphine's effect on the splanchnic circulation is complex. It has been suggested that

small doses of morphine may produce a decrease in central sympathetic activity with associated splanchnic vasodilation, while large doses of morphine may increase catecholamine release from the adrenal medulla, from sympathetic nerve endings, or both, (5) resulting in splanchnic vasoconstriction.

The effect of fentanyl on the splanchnic circulation has virtually not been studied. In dogs anesthetized with thiopental and nitrous oxide, fentanyl combined with droperidol (in doses that decreased cardiac output and blood pressure by approximately 30%) were accompanied by a parallel decrease in blood flow through the mesenteric artery and portal vein (8). It seems that the observed changes in preportal circulation were dependent on changes in the systemic circulation, resulting from the effect of droperidol rather than fentanyl (the latter does not decrease cardiac output or blood pressure) (1,2). Another study in rabbits showed that fentanyl was accompanied by a significantly increased blood pressure and decreased cardiac output, with no significant change in blood flow through the spleen and gastrointestinal tract (9). Unfortunately, hypoxia and hypercarbia developed in these animals and the circulatory changes apparently

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reflected the influence of hypoxia and hypercarbia rather than fentanyl per se.

This study was designed to evaluate the influence of narcotics, i.e., fentanyl and morphine, on the intestinal circulation in an isolated loop preparation, allowing determination of the direct and hormonal effects of narcotics on the peripheral circulation. Another objective of the study was to compare the clearance of rubidium with the entrapment of 9- $\mu$ m spheres to determine whether 9- $\mu$ m spheres entrapment reflects nutritive blood flow during the administration of narcotics, as it does under other conditions (10).

## Methods

Experiments were performed on 37 dogs weighing 15–20 kg. The dogs were anesthetized with sodium pentobarbital, 30 mg·kg<sup>-1</sup> intravenously. Controlled ventilation, adjusted to maintain arterial CO<sub>2</sub> tension at 35–40 mm Hg, was provided with an Air Shield ventilator through an endotracheal tube. Pancuronium, 0.1 mg·kg<sup>-1</sup>, was given for maintenance of muscle relaxation. Femoral arteries and veins were exposed and cannulated; 100 ml of blood was collected for future transfusion and replaced with 350 ml of Ringer's lactated solution. In addition, Ringer's lactated solution was also infused through the left femoral vein at a constant rate of 15 ml·kg<sup>-1</sup>·hr<sup>-1</sup>. A laparotomy was performed and a segment of the small intestine, supplied by a vascular arcade arising from a single mesenteric artery and vein, was selected. The isolated loop preparation (10) involved dissection of short segments of the mesentery artery and vein, free of the mesentery. Heparin, 5 mg·kg<sup>-1</sup>, was administered intravenously. The mesenteric vein was transected and cannulated with polyethylene tubing. Blood from the mesenteric vein was collected in a reservoir placed at the level of the mesenteric vein to achieve a 0 mm Hg mesenteric venous pressure. This blood was pumped back into the dog through a femoral vein. When the venous drainage was established, the artery was transected and cannulated, and arterial blood was pumped from the aorta through the intestinal segment (using a Holter precision roller pump) at a constant pressure of 100 mm Hg, maintained by adjusting the flow rate. The completely isolated loop was placed between saline-soaked gauzes and plastic wrap, and temperature was maintained at 37–38° C with an electrical pad.

Aortic pressure (via a femoral artery cannula) and perfusion pressure (pressure in arterial limb between pump and the intestinal segment) were recorded with Statham transducers and a Grass polygraph. After 30 min of stable perfusion and mean arterial pressures,

arterial and mesenteric venous blood samples were taken for pH and oxygen content determinations. A mixture of <sup>86</sup>Rb and 9- $\mu$ m spheres labeled with <sup>141</sup>Ce was then injected within 15 sec into the arterial cannula supplying the intestinal loop (the port of injection was placed between the femoral artery and the pump), while mesenteric venous blood was collected in test tubes for 3 min (15 sec per tube) for activity counting. After 3 min of blood collection, pump perfusion was terminated. The intestinal segment was divided into four to six pieces and processed for activity counting. Then, another intestinal segment was prepared and processed the same way. Blood drained from the mesenteric vein was replaced with blood that had been collected at the beginning of the experiment to maintain constant hematocrit values throughout the experiments. Two to four intestinal segments were used from each dog.

During each stage of measurements, analysis of arterial blood samples showed PaO<sub>2</sub> to be above 100 mm Hg, PaCO<sub>2</sub> between 35 and 40 mm Hg, and hematocrit between 30 and 35%. Observations with values not within these ranges were excluded from the study.

The first intestinal segment was studied under pentobarbital anesthesia in all 37 dogs. Then the dogs were divided into six groups: group 1 (control group, 4 dogs)—second, third and fourth loops were studied under pentobarbital anesthesia; group 2 (fentanyl, 6 dogs)—second loop was studied when fentanyl was injected intravenously, 10  $\mu$ g·kg<sup>-1</sup>, third loop was studied when an additional 20  $\mu$ g·kg<sup>-1</sup> of fentanyl was injected, and the fourth intestinal loop was studied when an additional 50  $\mu$ g·kg<sup>-1</sup> of fentanyl was given; group 3 (morphine, 6 dogs)—second loop was studied after morphine sulfate, 1 mg·kg<sup>-1</sup>, third loop was studied after an additional 2 mg·kg<sup>-1</sup> morphine, and the fourth loop was studied after an additional 5 mg·kg<sup>-1</sup>; group 4 (6 dogs)—second loop was studied after 5 mg·kg<sup>-1</sup> morphine intravenously; group 5 (5 dogs)—second loop was studied after cimetidine, 30 mg·kg<sup>-1</sup>, promethazine, 5 mg·kg<sup>-1</sup>, (to block H<sub>1</sub> and H<sub>2</sub> receptors) and morphine, 5 mg·kg<sup>-1</sup>. Cimetidine and promethazine were given simultaneously; morphine was injected 2–3 min later. Group 6 (5 dogs)—the second loop was studied after injection of phentolamine, 1 mg·kg<sup>-1</sup> (to block  $\alpha$ -adrenoceptors) and morphine, 5 mg·kg<sup>-1</sup>. Morphine was injected 2 min after phentolamine. Group 7 (5 dogs)—the second loop was studied after injection of promethazine, 5 mg·kg<sup>-1</sup>, cimetidine, 30 mg·kg<sup>-1</sup>, phentolamine, 1 mg·kg<sup>-1</sup> (to block H<sub>1</sub>, H<sub>2</sub> receptors and  $\alpha$ -adrenoceptors), and 5 mg·kg<sup>-1</sup> of morphine sulfate. Phentolamine, cimetidine, and promethazine were injected si-

multaneously, while morphine was given 2-3 min later.

Altogether, pentobarbital was studied in one (first) intestinal segment in all 37 dogs and in three additional segments in each of four dogs of group 1. Therefore, in group 1, 16 intestinal segments were studied during pentobarbital anesthesia (four dogs, four segments per dog). In group 2, six intestinal segments were studied during pentobarbital anesthesia and 18 intestinal segments during fentanyl anesthesia (six dogs, three different doses per dog). In group 3, six segments were studied under pentobarbital anesthesia and 18 intestinal segments were studied after morphine was given in incremental doses (six dogs, three segments per dog). In group 4, six intestinal segments were studied under pentobarbital effect only, and six other segments under morphine,  $5 \text{ mg} \cdot \text{kg}^{-1}$ . In group 5, five intestinal segments were studied under pentobarbital anesthesia in five dogs and then five additional intestinal segments were studied under the effect of morphine and histamine receptor antagonists. In group 6, five intestinal segments were studied during pentobarbital anesthesia and five additional segments were studied during  $\alpha$ -adrenoceptor blockade and morphine,  $5 \text{ mg} \cdot \text{kg}^{-1}$ . In group 7, five intestinal segments were studied during pentobarbital anesthesia and five additional segments were studied during  $\alpha$ -adrenoceptor blockade, histamine receptor blockade, and morphine,  $5 \text{ mg} \cdot \text{kg}^{-1}$ .

Phentolamine,  $1 \text{ mg} \cdot \text{kg}^{-1}$ , is accompanied by blockade of  $\alpha$ -adrenoceptors (11,12). Blockade of  $H_1$  and  $H_2$  receptors was achieved by promethazine,  $5 \text{ mg} \cdot \text{kg}^{-1}$ , and cimetidine,  $30 \text{ mg} \cdot \text{kg}^{-1}$ , respectively (13,14).

Ten to 15 minutes was required for the preparation of each isolated intestinal segment. An additional 10-15 min was needed to stabilize perfusion pressure. This period was followed by 30 min of stable perfusion and stable mean arterial pressures, and then another 5 min was required for blood sampling and injection of rubidium and microspheres. In the last three groups, measurements at the second loop were performed 9-12 min after phentolamine, cimetidine, or both, in combination with promethazine and morphine injection when the flow through the loop was adjusted by changing the flow rate to achieve perfusion pressure at 100 mm Hg.

Oxygen tension and pH were measured with an Instrumentation Laboratories (IL) model 813 pH/blood-gas analyzer. Oxygen content was measured with an IL 282 coximeter. Each shipment of microspheres (purchased from 3M Co., St. Paul, MN) was checked for size of spheres (determined with a Coulter Counter used for determination of red cell size), fragmenta-

tion, and aggregation (15). Microspheres were used only when size variations did not exceed standard deviations of  $1 \mu\text{m}$ . Microspheres were labeled with  $^{141}\text{Ce}$  and suspended in a 10% dextran with polysorbate (Tween 80). Microspheres were mixed in a special injector (15) with  $^{86}\text{Rb}$  and diluted in 3 ml of normal saline. Each injection contained about  $10^6$  of spheres and approximately  $300 \mu\text{Ci}$  of rubidium. Each of the isotopes generated approximately  $0.5 \times 10^6$  counts/min.

Radioactivity in the intestinal segment and mesenteric venous blood samples was analyzed with a Tracor 2250 gamma counting system (Tracor Northern, Middleton, WI). This system utilizes the least-squares "fitting" technique to resolve the amount of radioactivity contributed by each isotope ( $^{141}\text{Ce}$  and  $^{86}\text{Rb}$  in this case) in gamma ray spectra obtained by an NaI detector for the individual tissue and blood samples (10,16,17). The method employs an isotope calibration file that contains the decay rate, the number of counts per microspheres, and the spectral definition of each isotope used in the study. Once loaded into memory, this calibration file was used by the Microsphere Analysis Program to conduct a comparison of the spectra contained in the file (standard spectra) and the spectra of the blood or tissue sample.

Total blood flow in each intestinal segment was measured directly by the amount of blood drained from the mesenteric vein. Each segment was weighed after the experiment and blood flow (BF) calculated in  $\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ .

Vascular resistance (VR) was calculated as follows:  
VR ( $\text{mm Hg} \cdot \text{ml}^{-1} \cdot \text{min} \cdot \text{g}$ )

$$= \frac{\text{perfusion pressure (mm Hg)}}{\text{blood flow (ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1})}$$

Arteriovenous oxygen content difference ( $\text{AVDO}_2$ ) was calculated and expressed in  $\text{ml O}_2 \cdot \text{dl}^{-1}$  of blood. Oxygen uptake was calculated by multiplying intestinal blood flow by arteriovenous oxygen content differences. Rubidium and  $9\text{-}\mu\text{m}$  sphere clearances were calculated as follows:  $\text{Cl-Rb} = \text{BF} \times (\text{Rb injected} - \text{Rb venous})/\text{Rb injected}$ , and  $\text{Cl-Sph} = \text{BF} \times (\text{Sph injected} - \text{Sph venous})/\text{Sph injected}$ , where BF is intestinal blood flow in  $\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ ; Rb injected and Rb venous are rubidium activity injected into and recovered from the intestinal segment, respectively; and Sph injected and Sph venous are numbers of  $9\text{-}\mu\text{m}$  spheres injected into and recovered from the intestinal segment, respectively (10). Permeability-surface area product (PS) was calculated as follows (18):

$$\text{PS} = - \text{blood flow} \times \ln \left( 1 - \frac{\text{Rb injected} - \text{Rb venous}}{\text{Rb injected}} \right).$$



The activity injected into the segment was compared with activity found in the blood and intestinal segment.

Data are presented as means  $\pm$  standard errors of the mean. Differences between groups and control values (pentobarbital) were tested by the use of a one-way analysis of variance. Because the dogs within a particular treatment group were subjected to different doses of the same drug, differences between levels of the same drug were tested by use of a randomized block analysis. This allowed an adjustment for the between-dog variability when comparing dosage levels for the same drug. Individual comparisons between pairs of means were performed using Fisher's protected least significant difference test (19). Pearson's correlation coefficient and the corresponding least squares regression equation were used as the measure of association when comparing two response measurements. Differences were considered significant if  $P < 0.05$ . All computations were performed with the aid of the Statistical Analysis System (20).

## Results

The amounts of activity found in the intestinal segment and mesenteric venous blood did not differ from

the injected activity by more than 10%. The difference in the activity of  $^{141}\text{Ce}$  and  $^{86}\text{Rb}$  (calculated per gram of tissue) between samples of one intestinal loop never exceeded 10%. There were no significant differences between variables observed during the first, second, third, and fourth segment preparations in the control group. A strong and significant correlation was found between rubidium and microsphere clearances,  $r = 0.97$  (Fig. 1).

The main variables observed under the experimental conditions are presented in Table 1. There were no statistically significant differences in any variables observed between four subsequent intestinal loop preparations in control animals (group 1) anesthetized with pentobarbital. Fentanyl decreased oxygen uptake ( $\text{O}_2\text{up}$ ) and vascular resistance (VR) and increased blood flow (BF), rubidium clearance (Cl-Rb), microsphere entrapment (Cl-Sph) (Fig. 2), and permeability-surface area product (PS) in a dose-related fashion.

Morphine sulfate,  $1 \text{ mg}\cdot\text{kg}^{-1}$ , (group 3) had no significant effect on BF and VR compared with the pentobarbital group (group 1); however, it was accompanied by a slight, but statistically significant increase in microspheres entrapment, rubidium clear-

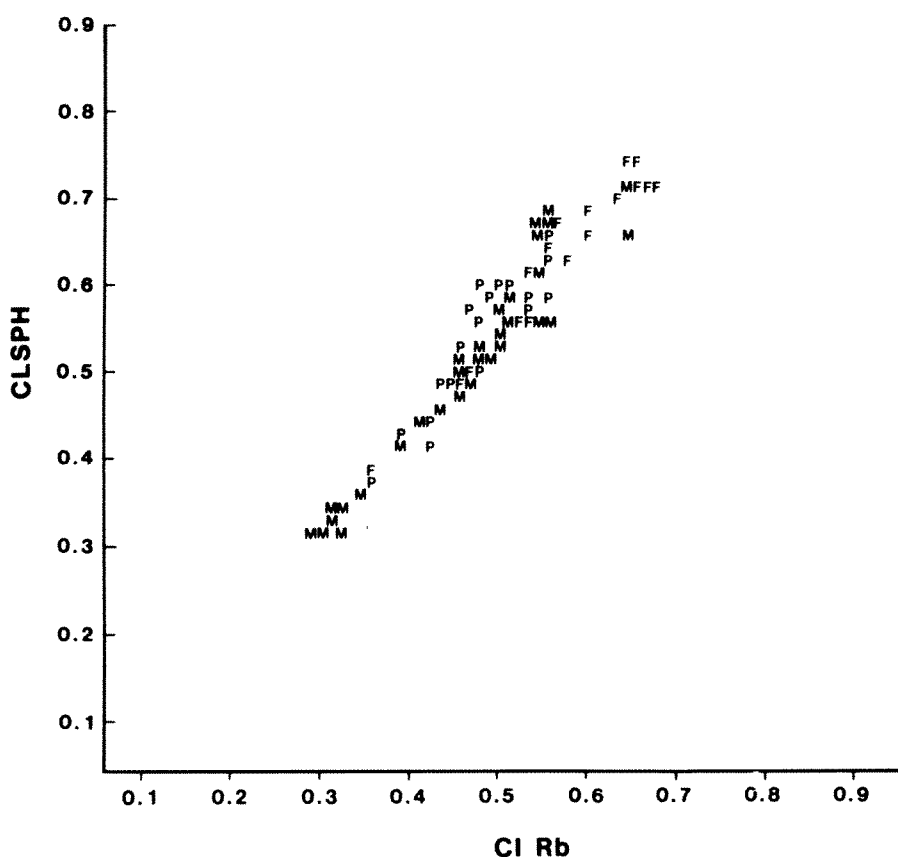


Figure 1. Plot of intestinal vascular clearance of  $9\text{-}\mu\text{m}$  spheres (Cl-Sph in  $\text{ml}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$ ) against rubidium clearance (Cl-Rb in  $\text{ml}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$ ). P, F, and M represent values observed during pentobarbital, fentanyl, and morphine, respectively.  $r = 0.97$ ,  $P < 0.001$ ;  $\text{Cl-Sph} = -0.031 \pm 1.165\cdot\text{Cl-Rb}$ .

Table 1. Opioids and Circulation in Isolated Intestinal Segment

Groups	BF	VR	AVDO <sub>2</sub>	O <sub>2</sub> up	Cl-Sph	Cl-Rb	PS
1. Pent	0.56 ± 0.01	182 ± 5	3.60 ± 0.11	2.0 ± 0.1	0.52 ± 0.01	0.47 ± 0.01	1.07 ± 0.03
2. F-10	0.61 ± 0.06	173 ± 21	2.62 ± 0.17 <sup>a</sup>	1.6 ± 0.2 <sup>a</sup>	0.59 ± 0.05 <sup>a</sup>	0.53 ± 0.05 <sup>a</sup>	1.24 ± 0.09 <sup>a</sup>
2. F-20	0.65 ± 0.05 <sup>a,b</sup>	161 ± 12 <sup>a</sup>	1.97 ± 0.16 <sup>a,b</sup>	1.3 ± 0.1 <sup>a,b</sup>	0.62 ± 0.04 <sup>a</sup>	0.56 ± 0.03 <sup>a,b</sup>	1.32 ± 0.07 <sup>a</sup>
2. F-50	0.70 ± 0.05 <sup>a,b,c</sup>	139 ± 10 <sup>a,b</sup>	1.03 ± 0.15 <sup>a,b,c</sup>	0.8 ± 0.1 <sup>a,b,c</sup>	0.66 ± 0.03 <sup>a,b,c</sup>	0.61 ± 0.03 <sup>a,b,c</sup>	1.41 ± 0.09 <sup>a,b,c</sup>
3. M-1	0.63 ± 0.04 <sup>d</sup>	163 ± 12 <sup>d</sup>	4.13 ± 0.42	2.5 ± 0.1 <sup>a,d</sup>	0.60 ± 0.04 <sup>a,d</sup>	0.54 ± 0.02 <sup>a,d</sup>	1.32 ± 0.08 <sup>a,d</sup>
3. M-1-5	0.50 ± 0.03	198 ± 10 <sup>d</sup>	3.10 ± 0.71 <sup>d</sup>	1.5 ± 0.3 <sup>a</sup>	0.48 ± 0.02 <sup>d</sup>	0.44 ± 0.01 <sup>d</sup>	1.11 ± 0.03 <sup>d</sup>
4. M-5	0.41 ± 0.04 <sup>a</sup>	252 ± 13 <sup>a</sup>	4.60 ± 0.28 <sup>a</sup>	1.8 ± 0.1	0.40 ± 0.03 <sup>a</sup>	0.36 ± 0.03 <sup>a</sup>	0.90 ± 0.05 <sup>a</sup>
5. M-5H	0.36 ± 0.01 <sup>a</sup>	283 ± 12 <sup>a</sup>	2.36 ± 0.10 <sup>a,d</sup>	0.9 ± 0.1 <sup>a,d</sup>	0.34 ± 0.01 <sup>a</sup>	0.32 ± 0.01 <sup>a</sup>	0.82 ± 0.03 <sup>a</sup>
6. M-5α	0.64 ± 0.04 <sup>a,d,e</sup>	164 ± 11 <sup>a,d,e</sup>	2.30 ± 0.73 <sup>a,d</sup>	1.4 ± 0.3 <sup>a,d,e</sup>	0.61 ± 0.04 <sup>a,d,e</sup>	0.52 ± 0.02 <sup>a,d,e</sup>	1.12 ± 0.06 <sup>a,d,e</sup>
7. M-5αH	0.58 ± 0.02 <sup>d,e</sup>	172 ± 4 <sup>d,e</sup>	3.25 ± 0.40 <sup>d</sup>	1.9 ± 0.2 <sup>e</sup>	0.52 ± 0.01 <sup>d,e,f</sup>	0.48 ± 0.01 <sup>d,e</sup>	1.00 ± 0.02

Values are given as means ± SEM. Abbreviations: BF, blood flow in ml·min<sup>-1</sup>·g<sup>-1</sup>; VR, vascular resistance in the intestinal segment in mm Hg·m<sup>-1</sup>·min·g; AVDO<sub>2</sub>, arteriovenous oxygen content difference in ml of oxygen in 100 ml of blood; O<sub>2</sub>up, oxygen uptake in ml O<sub>2</sub>·min<sup>-1</sup>·100 g<sup>-1</sup>; Cl-Sph, microsphere clearance (entrapment) in ml·min<sup>-1</sup>·g<sup>-1</sup>; Cl-Rb, rubidium clearance in ml·min<sup>-1</sup>·g<sup>-1</sup>; PS, permeability surface area product; Pent, pentobarbital; F-10, F-20, F-50—fentanyl, 10 μg·kg<sup>-1</sup>, 20 μg·kg<sup>-1</sup>, 50 μg·kg<sup>-1</sup>, respectively; M-1, morphine, 1 mg·kg<sup>-1</sup>; M-1-5, morphine, 5 mg·kg<sup>-1</sup>, given after 1 and 2 mg·kg<sup>-1</sup> of morphine; M-5, morphine, 5 mg·kg<sup>-1</sup>; M-5H, morphine, 5 mg·kg<sup>-1</sup>, plus H<sub>1</sub> and H<sub>2</sub> receptor blockade; M-5α, morphine, 5 mg·kg<sup>-1</sup>, plus α-adrenoceptor blockade; M-5αH, morphine, 5 mg·kg<sup>-1</sup>, plus α-adrenoceptor blockade plus H<sub>1</sub> and H<sub>2</sub> receptor blockade.

<sup>a</sup>P < 0.05 vs group 1, pentobarbital.

<sup>b</sup>P < 0.05 vs group 2, F-10.

<sup>c</sup>P < 0.05 vs group 2, F-20.

<sup>d</sup>P < 0.05 vs group 4, M-5.

<sup>e</sup>P < 0.05 vs group 5, M-5H.

<sup>f</sup>P < 0.05 vs group 6, M-5α.

ance, and PS. Morphine sulfate, 5 mg·kg<sup>-1</sup>, given on the top of the dose of 1 mg·kg<sup>-1</sup> and 2 mg·kg<sup>-1</sup> (total dose 8 mg·kg<sup>-1</sup>, group 3) was accompanied by values similar to those observed during pentobarbital anesthesia and different from values observed under the effect of 1 mg·kg<sup>-1</sup> of morphine: values of vascular resistance were significantly higher; and blood flow, microsphere entrapment, rubidium clearance, and PS were significantly lower under 5 mg·kg<sup>-1</sup> than under 1 mg·kg<sup>-1</sup> morphine in this group.

Morphine sulfate, 5 mg·kg<sup>-1</sup>, per se (group 4, studied without previously given morphine) was accompanied by vascular resistance that was significantly higher; and blood flow, microspheres entrapment, rubidium clearance, and PS that were significantly lower than with either pentobarbital or 1 mg·kg<sup>-1</sup> of morphine (Table 1, Fig. 3). The same dose of morphine (5 mg·kg<sup>-1</sup>), in the presence of H<sub>1</sub> and H<sub>2</sub> receptor blockade with cimetidine and promethazine (group 5), was associated with a significantly higher

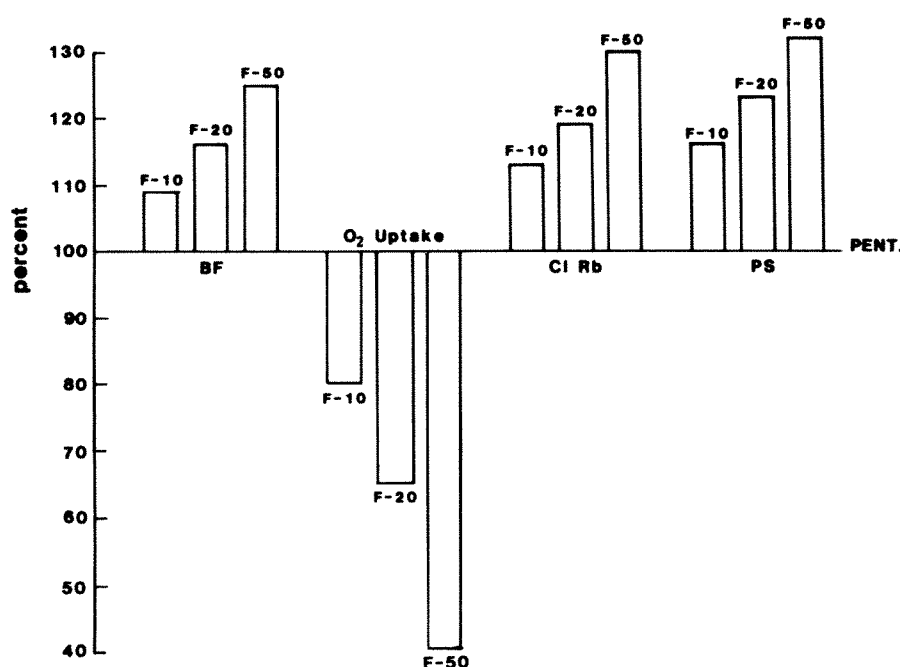


Figure 2. Effect (percent change) of fentanyl on intestinal blood flow (BF), oxygen uptake (O<sub>2</sub> uptake), rubidium clearance (Cl-Rb), and permeability-surface area product (PS). Abbreviations: PENT, pentobarbital anesthesia (100%); F-10, F-20, and F-50—fentanyl, 10 μg·kg<sup>-1</sup>, 20 μg·kg<sup>-1</sup>, and 50 μg·kg<sup>-1</sup>, respectively. Absolute values and levels of significance are presented in Table 1.

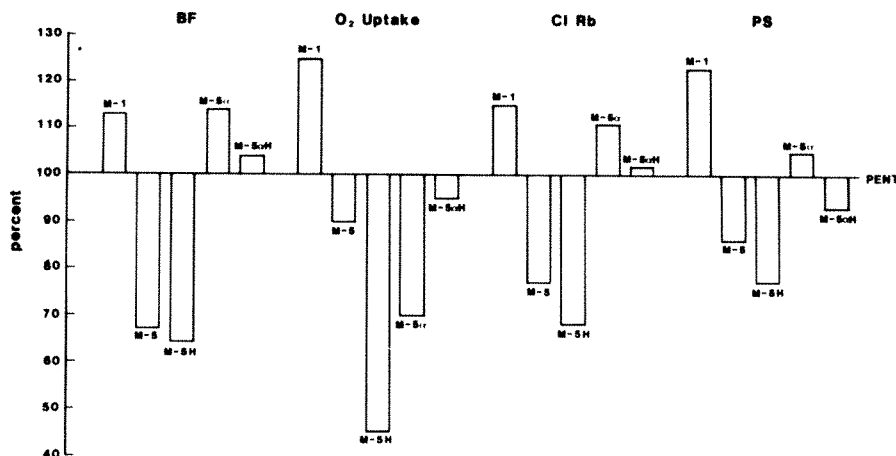


Figure 3. Effect (percent change) of morphine on intestinal blood flow (BF), oxygen uptake (O<sub>2</sub> uptake), rubidium clearance (Cl-Rb), and permeability-surface area product (PS). Abbreviations: PENT, pentobarbital anesthesia (100%); M-1, morphine, 1 mg·kg<sup>-1</sup>; M-5, morphine, 5 mg·kg<sup>-1</sup>; M-5H, morphine, 5 mg·kg<sup>-1</sup>, plus H<sub>1</sub> and H<sub>2</sub> receptor blockade; M-5α, morphine, 5 mg·kg<sup>-1</sup>, plus α-adrenoceptor blockade; M-5αH, morphine 5 mg·kg<sup>-1</sup>, plus α-adrenoceptor blockade, plus H<sub>1</sub> and H<sub>2</sub> receptor blockade. Absolute values and levels of significance are presented in Table 1.

resistance and lower flow, microsphere entrapment, rubidium clearance, and PS, than was pentobarbital. Values of AVDO<sub>2</sub> and O<sub>2</sub>up in group 5 (morphine plus H<sub>1</sub> and H<sub>2</sub> receptor blockade) were significantly lower than in groups 1 and 4 (Fig. 3).

BF, Cl-Sph, Cl-Rb, and PS after morphine, 5 mg·kg<sup>-1</sup>, given during α-adrenoceptor blockade achieved with phentolamine (group 6) were significantly higher, and values of VR, AVDO<sub>2</sub> and O<sub>2</sub>up were significantly lower, than in the pentobarbital-treated group (group 1). On the other hand, BF, Cl-Sph, and Cl-Rb were significantly higher, and values of VR, and AVDO<sub>2</sub> were significantly lower during combined α-adrenoceptor blockade and H<sub>1</sub> and H<sub>2</sub> receptor blockade (group 7), than in animals that received morphine per se (group 4). Blood flow, microsphere entrapment, rubidium clearance, and PS were significantly lower under morphine, 5 mg·kg<sup>-1</sup>, alone (group 4), than when morphine was given during α-adrenoceptor and H<sub>1</sub> and H<sub>2</sub> blockade (group 7).

## Discussion

The discussion provides the justification of the methodology used in this study, and is followed by the interpretation of the observed data with possible clinical implications.

Rubidium is highly diffusible across exchange vessels, which means that most of the substance presented in the exchange vessels is absorbed by tissues. Consequently, the ratio of absorbed to nonabsorbed rubidium would represent the ratio of the blood flow through nutritive vessels to flow through nonnutritive vessels. The results of the present study (strong correlation between microspheres and rubidium clearances) demonstrate that 9-μm spheres and rubidium behave in the vascular bed in a similar way,

i.e., spheres are trapped and rubidium is absorbed in the nutritive exchange vessels and shunted through nonnutritive vessels where exchange does not occur, or occurs to a limited extent. The results agree with previously demonstrated data (10,21) that the shunting of 9-μm spheres through tissue reflects the arteriovenous shunting of blood and, therefore, can be used as a tool to study nutritive and nonnutritive blood flow in tissues during anesthesia with opioids. It remains to be seen which vessels (arteriovenous anastomoses, thoroughfare channels, or even distended capillaries) are involved in the arteriovenous shunting of spheres, rubidium, and blood.

Similar activities found in different pieces of each intestinal loop show adequate mixing of spheres and rubidium in the blood stream. The perfusion of the intestinal segment by a pump with constant pressure assured independence of the intestinal circulation from the systemic circulation, while complete isolation of the segment assured independence of the intestinal circulation from the neural regulatory mechanisms. Thus this preparation allowed us to study the direct influence of anesthetics on the intestinal circulation as well as indirect effects related to various hormonal factors, e.g., epinephrine, histamine.

Changes in PS in the present study mimicked alterations in Cl-Rb. Apparently, it might mean that the changes in PS were related to changes in surface area (number of perfused capillaries), but not to altered permeability.

Regional blood flow is regulated by many factors (local, nervous, and humoral) that affect the circulation directly and indirectly (22). Therefore, it seems that changes in the splanchnic circulation observed during anesthesia with narcotics can be, on one hand, a reflection of compensatory processes devoted to maintain the systemic circulation and homeostasis or,



on the other hand, can reflect other indirect (nervous and humoral) or direct effects of narcotics on the splanchnic circulation.

Fentanyl induced a dose-dependent decrease in intestinal vascular resistance and an increase in flow, microspheres entrapment, rubidium clearance, and PS. These changes were accompanied by a substantial and dose-related decrease in intestinal oxygen uptake. The decrease in oxygen consumption was twice the increase in microsphere entrapment, rubidium clearance, and PS (Fig. 2). Obviously, "luxury perfusion" developed in the intestinal loop under the influence of fentanyl in a dose-related fashion: the increase in total (measured directly) and nutritive (determined by CI-Rb) flows was accompanied by a substantial decrease in oxygen uptake. Clinical implications of these data are not clear. However, we may hypothesize that a decrease in intestinal oxygen uptake with a concomitant increase in flow and reduction in arteriovenous oxygen content difference would increase mesenteric venous and portal venous oxygen content, thereby improving hepatic oxygen supply.

The effect of morphine on the intestinal vasculature is more complex than the effect of fentanyl. Small doses of morphine ( $1 \text{ mg} \cdot \text{kg}^{-1}$ ) led to a significant increase in nutritive BF with no changes in total (nutritive and nonnutritive) BF: CI-Sph, CI-Rb, and PS were significantly greater (by 15–23%) than during pentobarbital anesthesia, while directly measured total BF and calculated VR did not differ significantly from control values. High doses of morphine ( $5 \text{ mg} \cdot \text{kg}^{-1}$ ) were accompanied by obvious vasoconstriction: calculated VR was increased while BF, CI-Sph, CI-Rb, and PS were significantly decreased compared with control (pentobarbital anesthesia) values.

Epinephrine increases or does not change intestinal oxygen uptake (23) and increases capillary density (24). It has been suggested that arteries regulate blood flow and thus govern the flux of oxygen into the capillaries, whereas precapillary sphincters control the number of capillaries perfused at a given time and thus govern the diffusive flux of oxygen to tissues (23). Compared to pentobarbital, morphine,  $5 \text{ mg} \cdot \text{kg}^{-1}$ , decreased BF, CI-Sph, and CI-Rb to approximately similar degrees (23–27%) with no significant changes in intestinal oxygen uptake. Apparently morphine in this dose constricted arteries, but did not change oxidative metabolism. The vasoconstriction was completely abolished by  $\alpha$ -adrenoceptor blockade (Fig. 3). Thus it appears that morphine affected the intestinal circulation by release of epinephrine. It has been shown that morphine can increase the release of epinephrine from the adrenal medulla (25,26) and the release of histamine (25,27,28).

Catecholamine release from the adrenal medulla can be mediated through histamine. However, this effect is observed only during very substantial increases in histamine levels (29–31), not during moderate increases in histamine concentrations (32). Our data do not support the possibility that morphine-induced catecholamine release is due to histamine-mediated effect:  $H_1$  and  $H_2$  receptor blockade did not abolish morphine-induced intestinal vasoconstriction. Thus our data demonstrate that the vasoconstricting effect of  $5 \text{ mg} \cdot \text{kg}^{-1}$  of morphine results from a release of catecholamines, apparently from the adrenal medulla.

The vasodilating effect of morphine observed at a low dose of morphine,  $1 \text{ mg} \cdot \text{kg}^{-1}$ , might be related to histamine release for the following reasons. First, blood flow was probably slightly higher when  $5 \text{ mg} \cdot \text{kg}^{-1}$  of morphine was given during  $\alpha$ -adrenoceptor blockade than when the same dose of morphine was given during combined  $\alpha$ -adrenoceptor and  $H_1$  and  $H_2$  receptor blockade. The difference between the values of these two groups was statistically insignificant; however, microsphere entrapment during  $\alpha$ -adrenoceptor blockade with  $5 \text{ mg} \cdot \text{kg}^{-1}$  of morphine was significantly greater than during injection of  $5 \text{ mg} \cdot \text{kg}^{-1}$  of morphine in the presence of  $\alpha$ -adrenoceptor,  $H_1$  and  $H_2$  receptor blockade. Second, there was a tendency to a more pronounced vasoconstriction when  $5 \text{ mg} \cdot \text{kg}^{-1}$  of morphine was given during  $H_1$  and  $H_2$  receptor blockade than with the same dose of morphine alone (differences between these two groups did not reach a level of statistical significance). The vasodilating effect of morphine on the splanchnic vasculature has been demonstrated (5–7). The mechanism of vasodilating influence is not clear; it certainly can be related to histamine release. Our data do fit this hypothesis, but due to lack of statistical significance do not substantiate it clearly.

It is interesting to note that intestinal oxygen uptake was less in group 5 where  $H_1$  and  $H_2$  receptor blockade was present in combination with  $5 \text{ mg} \cdot \text{kg}^{-1}$  of morphine than in groups 4 and 7 ( $5 \text{ mg} \cdot \text{kg}^{-1}$  of morphine alone, and  $5 \text{ mg} \cdot \text{kg}^{-1}$  of morphine combined with  $\alpha$ -adrenoceptor and  $H_1$  and  $H_2$  receptor blockade). This difference can be partially explained by the difference in intestinal oxygen demand between the groups.  $H_1$  and  $H_2$  receptor blockade is associated with decreased intestinal motility, and therefore, reduced intestinal oxygen demand and uptake (33). On the other hand,  $\alpha$ -adrenoceptor blockade results in increased intestinal motility (34), with subsequent enhanced oxygen demand.

The present data suggest that changes in the intestinal circulation during anesthesia with opioids might

play a certain role in the cardiovascular homeostasis during anesthesia and surgery. Fentanyl, as well as morphine combined with  $H_1$  and  $H_2$  receptor blockade, substantially decreased intestinal oxygen uptake and arteriovenous oxygen content difference. A subsequent increase in oxygen content in portal venous blood should improve hepatic oxygenation.

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## Safety and Efficacy of Epinephrine Added to Bupivacaine for Lumbar Epidural Analgesia in Obstetrics

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ABBOUD TK, SHEIK-OL-ESLAM A, YANAGI T, MURAKAWA K, COSTANDI J, ZAKARIAN M, HOFFMAN D, HAROUTUNIAN S. Safety and efficacy of epinephrine added to bupivacaine for lumbar epidural analgesia in obstetrics. *Anesth Analg* 1985;64:585-91.

*The effects of epidural bupivacaine with and without 1:300,000 epinephrine on uterine activity, progress of labor, fetal heart rate, maternal blood pressure and heart rate, newborn Apgar scores, neonatal acid-base status, and Neurologic and Adaptive Capacity Scoring System (NACS) were compared in 32 parturients during labor and delivery. Patients in group I (n = 16) received 0.5% bupivacaine with 1:300,000 epinephrine and those in group II (n = 16) received 0.5% bupivacaine alone. Addition of epinephrine to bupivacaine had no significant effects on uterine activity, duration of first or second stages of labor, fetal heart rate*

*and variability, or the incidence of abnormal fetal heart rate patterns. Maternal hypotension occurred less frequently in group I than in group II patients ( $P < 0.05$ ). Apgar scores, neonatal acid-base status, and the NACS were equally good in the two groups. Duration of analgesia was significantly longer in group I than in group II ( $186.8 \pm 11.6$  vs  $85.3 \pm 6.1$  (mean  $\pm$  SEM) min,  $P < 0.001$ ). It is concluded that adding epinephrine to bupivacaine during epidural anesthesia in the normal parturient has no adverse effects on either mother, fetus, neonate, or the progress of labor; and that it significantly prolongs the duration of anesthesia and decreases the incidence of maternal hypotension.*

**Key Words:** ANESTHESIA—obstetrics. ANESTHETIC TECHNIQUES—epidural. ANESTHETICS, LOCAL—bupivacaine.

Several cases have been reported by the FDA in which bupivacaine was apparently administered unintentionally intravenously, and in which cardiac arrest was preceded by convulsions and followed by encephalopathy and/or death (1). In none of these cases did the local anesthetic solutions contain epinephrine. Recently Moore et al. (2) demonstrated that the stimulatory action of epinephrine added to bupivacaine can protect against or correct the depressant effects of bupivacaine on the myocardium. However, many anesthesiologists avoid injecting epinephrine in the parturient because of its possible adverse effects on uterine contractions and uterine blood flow.

We recently reported that adding epinephrine, 1:300,000 to lidocaine during epidural anesthesia in the normal parturient has no adverse maternal or neonatal effects, and it significantly prolongs the duration

of anesthesia and limits the placental transfer of lidocaine (3). The present study was undertaken to evaluate maternal and neonatal effects of epinephrine added to bupivacaine during lumbar epidural anesthesia.

### Methods and Materials

Thirty-two parturients at term with no obstetric or medical complications who elected to have epidural anesthesia for labor and delivery were studied. The study was approved by the Committee on Human Experimentation, and informed consents were obtained from all patients. All patients had ruptured membranes. Utilizing a Corometrics 112 fetal monitor, uterine activity was monitored with a transcervical intrauterine catheter and fetal heart rate (FHR) was directly monitored with a scalp electrode. Fetal heart rate variability was also recorded using the template of Hon (4). Maternal heart rate and blood pressure were monitored throughout the study using an automated blood pressure device. Before induction of epidural anesthesia, all fetuses had normal fetal heart rate patterns.

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Table 1. Patient Data

	Group I Bupivacaine with epinephrine	Group II Bupivacaine alone
Maternal age (yr)	25.6 ± 1.6	23.1 ± 1.4
Maternal weight (kg)	65.9 ± 2.1	65.6 ± 1.9
Maternal height (cm)	157.4 ± 1.6	155.9 ± 0.9
Gestational age (wk)	39.6 ± 0.4	40.9 ± 0.5
Infant weight (g)	3417 ± 119	3484 ± 115

Values are mean ± SEM.

No significant differences between groups by Student's *t*-test.

With patients in the left lateral decubitus position, epidural catheters were placed at L3-4 interspace and advanced 2 cm cephalad. Patients were then placed in the lateral position and were encouraged to remain in the same position throughout the study. All patients were given 500 ml of 5% dextrose in lactated Ringer's solution and, after measurement of FHR, fetal heart rate variability, uterine activity, maternal blood pressure, and heart rate for 30 min, patients were given one of two local anesthetic solutions in a random manner. Patients in group I (*n* = 16) received 0.5% bupivacaine with 1:300,000 epinephrine, those in group II (*n* = 16) received 0.5% bupivacaine alone. If, 5 min after a test dose of 2 ml of local anesthetic was injected, there was no evidence of subarachnoid injection, the remainder of the local anesthetic was injected. The dose was chosen to provide analgesia to a level of T10.

Local anesthetics were reinjected as clinically indicated and observations continued until delivery of the infant. Duration of analgesia after each loading dose of the local anesthetic was defined as the time from onset of pain relief until the time of onset of discomfort. The overall quality of analgesia was evaluated using our routine scale ranging from 0 for no pain relief to 4+ representing excellent analgesia. Maternal hypotension was considered to be present whenever systolic blood pressure decreased more than 30 torr or to less than 100 torr. Hypotension was corrected by increasing the rate of intravenous fluid infusion and by administration of intravenous ephedrine. Duration of first and second stages of labor and the mode of delivery were noted. Maternal venous blood was drawn 10 min after administration of local anesthetic for determination of local anesthetic levels. Also, at the time of delivery blood was drawn from a maternal vein and from the umbilical artery and vein of a doubly clamped segment of the umbilical cord for measurement of local anesthetic levels. All samples were put into heparinized Vacutainers and put on ice. The plasma was removed after centrifugation and frozen until assayed for drug levels.

Table 2. Clinical Data

	Group I ( <i>n</i> = 16) Bupivacaine with epinephrine	Group II ( <i>n</i> = 16) Bupivacaine alone
Number of patients with hypotension	1	8 <sup>a</sup>
Duration (min)		
Analgesia	186.8 ± 11.6 <sup>b</sup>	85.3 ± 6.1
1st stage (> 4-10 cm)	133.2 ± 26.5	198.4 ± 61.9
2nd stage	119.8 ± 94.9	91.1 ± 26.2
Mode of delivery		
Spontaneous	10	12
Forceps and vacuum	3	3
Cesarean	3	1

Values are mean ± SEM.

<sup>a</sup>*P* < 0.025.<sup>b</sup>*P* < 0.001.

gation and frozen until assayed for drug levels. Neonates were evaluated by Apgar scores at 1 and 5 min, umbilical venous and arterial blood acid base status, and the Neurologic and Adaptive Capacity Scoring System at 15 min, and at 2 and 24 hr of age, according to a previously described protocol (5). Apgar scores were assigned by pediatricians who were unaware of which local anesthetic solution was administered. The NACS examination was performed by a trained anesthesia research fellow. The NACS gives a total score, the maximum being 40. Arbitrarily choosing 35 to 40 as the score denoting a vigorous baby (5), we determined the percentages of infants scoring 35 or higher and compared these in each group at 15 min, and at 2 and 24 hr of age. We also determined the percentage of infants having high scores on each of the individual test items. Those who evaluated FHR patterns, uterine activity, and the neonate were unaware of which of the local anesthetic solutions was administered.

Data were analyzed for statistical significance using Student's *t*-test and  $\chi^2$  when appropriate. A *P* value of less than 0.05 was considered statistically significant.

## Results

Data on maternal age, weight, height, infant's gestational age and weight are summarized in Table 1. There were no significant differences between the two groups.

### Effects on the Mother

Clinical results are shown in Table 2. Nine patients developed hypotension (one in group I and eight in group II). The incidence was statistically different between the groups (*P* < 0.05). Mean systolic arterial blood pressure decreased significantly (*P* < 0.05) be-

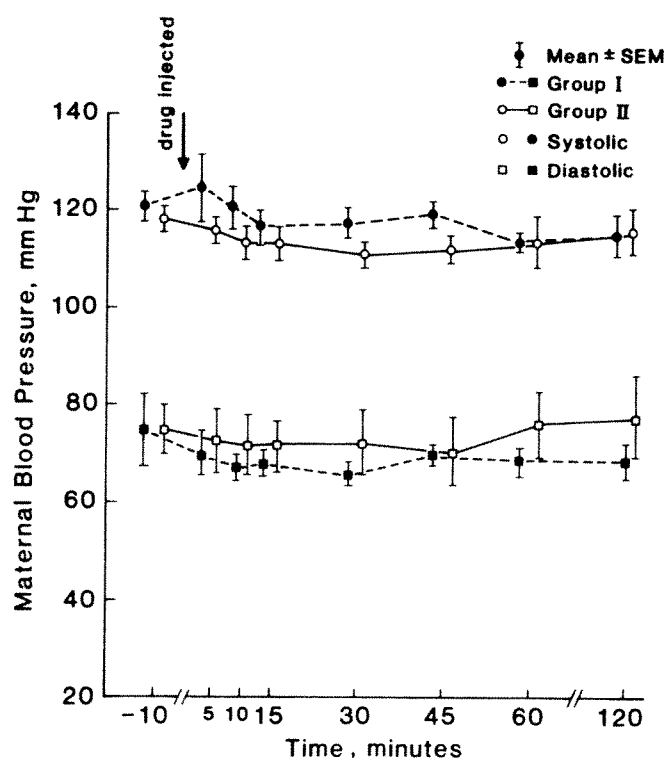


Figure 1. Effects of epidural anesthesia on maternal systolic and diastolic blood pressures (mean  $\pm$  SEM) in group I ( $n = 16$ ) and group II ( $n = 16$ ) patients. There was a statistically significant decrease in systolic blood pressure in group II patients 30 min after injection of local anesthetic ( $P < 0.05$ ) as determined by Student's  $t$ -test.

low baseline values 30 min after administration of the local anesthetic in group II patients; no changes were observed in group I patients (Fig. 1). Maternal heart rate did not change significantly in either group (Fig. 2). The quality of analgesia was either 3+ or 4+ in all patients in both groups. Duration of analgesia was significantly longer in group I patients than in group II patients ( $P < 0.001$ ). Duration of first and second stages of labor as well as the mode of delivery did not differ significantly in the two groups. Three patients in group I and one in group II underwent cesarean section due to failure to progress; the incidence was not significantly different between the two groups.

#### Effects on Uterine Activity

Uterine activity as measured by Montevideo units did not change significantly in any of the patients in either group, nor did it differ significantly in the two groups (Fig. 3).

#### Effects on the Fetal Heart Rate Parameters

Two fetuses in group I and six in group II developed tachycardia; five fetuses in group I and four in group

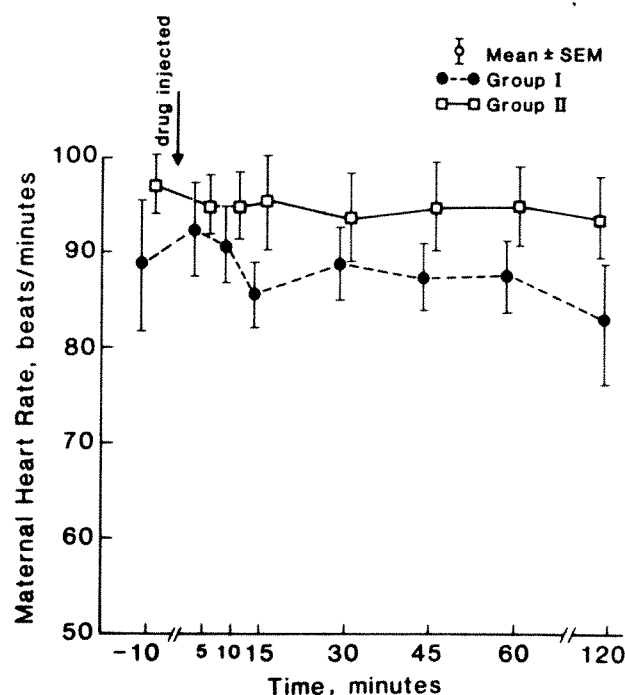


Figure 2. Effects of epidural anesthesia on maternal heart rate (mean  $\pm$  SEM) in group I ( $n = 16$ ) and group II ( $n = 16$ ) patients. No changes were statistically significant by Student's  $t$ -test.

II had abnormal heart rate patterns as defined by Kubli and Hon (6). These incidences were not significantly different between the two groups. Mean fetal heart rate (Fig. 4) or fetal heart rate variability (Fig. 5) did not change significantly in either group.

#### Maternal and Fetal Plasma Anesthetic Levels

Plasma levels of local anesthetics are presented in Table 3. There were no significant differences between the two groups.

#### Effects on the Newborn

There were no significant differences for the incidence of low 1 and 5 min Apgar scores between the two groups. Two neonates in each group had low 1 min Apgar scores, and one neonate in group II had a low 5 min Apgar score.

#### Umbilical Artery and Vein Blood Acid-Base Status

Umbilical arterial and venous acid-base status was within normal limits in the two groups (Table 4).

#### Neurologic and Adaptive Capacity Scores

The NACS scores of the two groups of neonates are presented in Table 5. The NACS was determined only

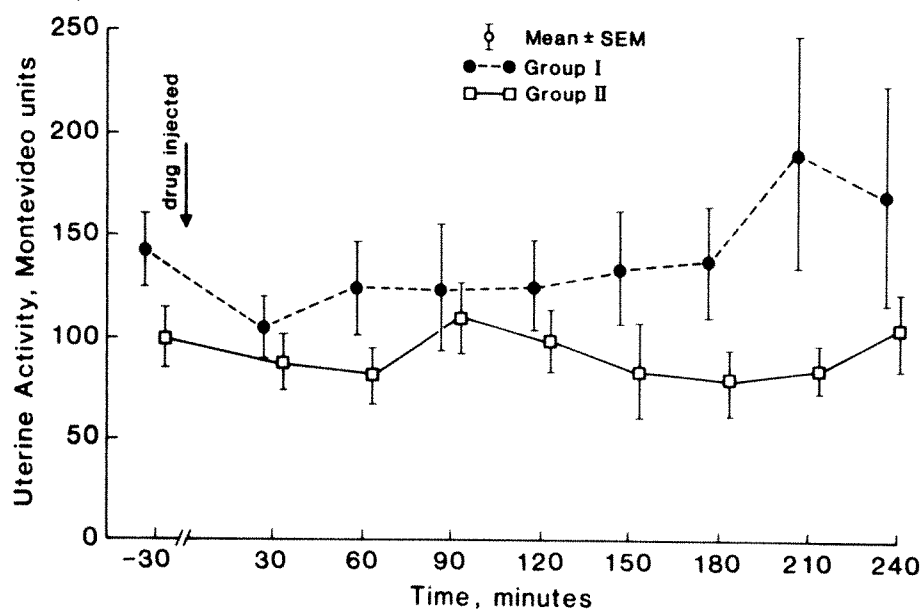


Figure 3. Effects of epidural anesthesia on uterine activity (mean  $\pm$  SEM) in group I ( $n = 16$ ) and group II ( $n = 16$ ) patients. No changes were statistically significant by Student's *t*-test.

in babies whose mothers had normal spontaneous or low forceps deliveries. There were no significant differences between the two groups in test scores for any test item on the NACS. The percentage of infants who scored 35-40 on the NACS was not significantly different in the two groups.

## Discussion

Our study demonstrates that addition of small doses of epinephrine to bupivacaine during lumbar epidural anesthesia in normal parturients significantly prolonged the duration of analgesia, did not affect the progress of labor, and decreased the incidence of maternal hypotension. While we have no apparent explanation for the lower incidence of hypotension in the epinephrine containing group, this might have been due to the  $\alpha$ -adrenergic effects of epinephrine, which slightly increases systemic vascular resistance and to the  $\beta$ -adrenergic effects with slight positive inotropic effects (7-11). Other possible advantages of adding epinephrine to local anesthetics during lumbar epidural anesthesia are prompt detection of intravascular injection and protection from cardiovascular toxic reactions to local anesthetics (12). Moore et al. (2) reported three cases of accidental intravascular injection of bupivacaine, one with and two without epinephrine. The patient who received the solution containing epinephrine had no cardiovascular depression, while the other two patients had cardiac arrest. The authors concluded that the stimulatory action of epinephrine added to bupivacaine can protect against or correct the depressant effect of this

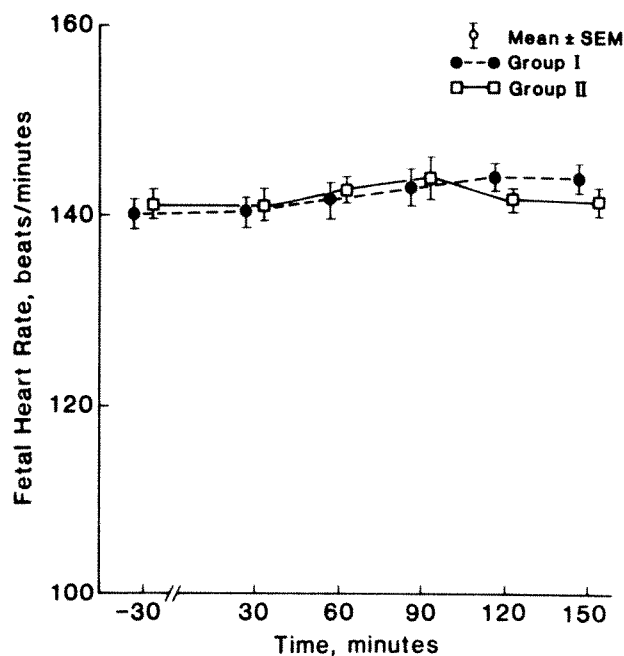


Figure 4. Effects of epidural anesthesia on fetal heart rate (mean  $\pm$  SEM) in group I ( $n = 16$ ) and group II ( $n = 16$ ) patients. No changes were statistically significant by Student's *t*-test.

agent on the myocardium. Therefore, to detect and prevent intravascular injection of large amounts of local anesthetics, we recommend adding a small amount of epinephrine to local anesthetic solutions during lumbar epidural analgesia in the healthy obstetrical patient.

The addition of epinephrine to local anesthetics has been shown, in this study as well as in others (3,13-15),



Figure 5. Effects of epidural anesthesia on fetal heart rate variability (mean  $\pm$  SEM) in group I ( $n = 16$ ) and group II ( $n = 16$ ) patients. No changes were statistically significant by Student's  $t$ -test.

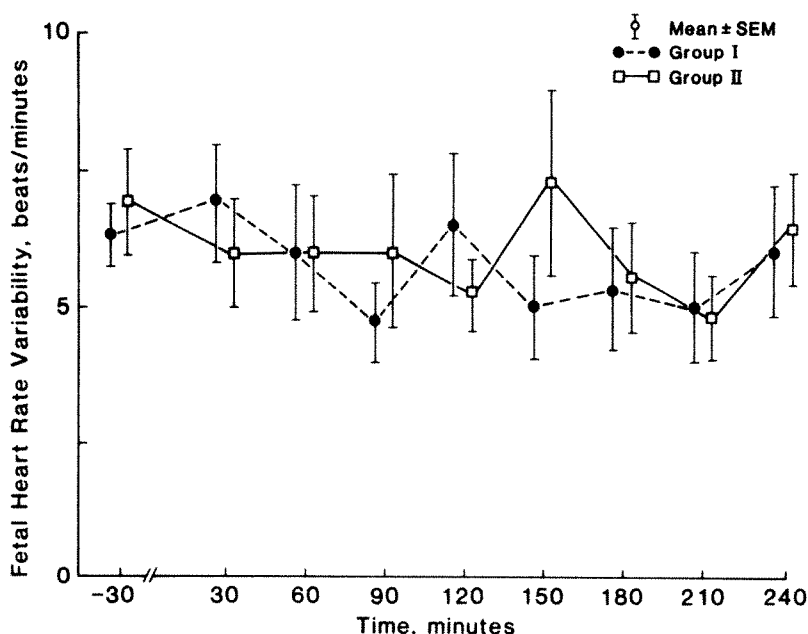


Table 3. Plasma Concentrations of Bupivacaine ( $\mu\text{g/ml}$ )

	Group I Bupivacaine with epinephrine	Group II Bupivacaine alone
Maternal vein		
10 min after injection	0.56 $\pm$ 0.07 (13) <sup>a</sup>	0.43 $\pm$ 0.04 (16)
At time of delivery	0.57 $\pm$ 0.17 (13)	0.45 $\pm$ 0.12 (15)
Umbilical vein	0.19 $\pm$ 0.10 (13)	0.15 $\pm$ 0.04 (15)
Umbilical artery	0.17 $\pm$ 0.10 (12)	0.13 $\pm$ 0.04 (13)
Umbilical vein/maternal vein (at time of delivery)	0.27 $\pm$ 0.12 (13)	0.31 $\pm$ 0.08 (15)

Values are mean  $\pm$  SEM.

No significant differences between groups by Student's  $t$ -test.

<sup>a</sup>Number of samples in parentheses.

Table 4. Acid Base and Blood Gas Data

	Group I Bupivacaine with epinephrine	Group II Bupivacaine alone
Umbilical Vein		
No.	13	15
pH	7.31 $\pm$ 0.02	7.32 $\pm$ 0.01
PO <sub>2</sub> (torr)	25.8 $\pm$ 1.5	26.9 $\pm$ 1.62
PCO <sub>2</sub> (torr)	39.3 $\pm$ 2.2	37.7 $\pm$ 1.1
Base excess (mEq/L)	-5.1 $\pm$ 0.7	-5.1 $\pm$ 0.5
Umbilical Artery		
No.	12	15
pH	7.25 $\pm$ 0.01	7.26 $\pm$ 0.02
PO <sub>2</sub>	18.2 $\pm$ 2.0	17.1 $\pm$ 0.9
PCO <sub>2</sub>	46.6 $\pm$ 1.9	49.1 $\pm$ 1.5
Base excess (mEq/L)	-5.6 $\pm$ 0.6	-2.9 $\pm$ 1.2

to improve the duration (3) and the quality of epidural anesthesia; however, many anesthesiologists and obstetricians avoid using epinephrine in the obstetrical patient due to its possible adverse effects on the uterine activity and uterine blood flow.

Findings from the present study demonstrate that the addition of small doses of epinephrine (26  $\mu\text{g}$ ) to bupivacaine has no adverse effects on the progress of labor. This is in agreement with our previous finding using lidocaine with epinephrine for lumbar epidural anesthesia in the parturient (3). The factors accounting for the observed differences in the results of our study, and other studies, are discussed in detail in our previous paper (3), including the relatively small dose of epinephrine used in our study compared to doses used in other studies (16-18), the different routes of administration—for instance in two studies epinephrine was given either intravenously or intra-

muscularly and was found to decrease uterine activity (19,20). Also, species differences (21) might have been a factor accounting for the observed differences.

In the present study we did not measure uterine blood flow, but we evaluated the effects of the added epinephrine on the fetus and neonate and found no deleterious effects. More recently, using <sup>133</sup>Xe technique, Albright et al. (22) and Jouppila et al. (23,24) found no significant changes in intervillous blood flow when 40-100  $\mu\text{g}$  of epinephrine was added to local anesthetics for lumbar epidural anesthesia in pregnant women.

On the basis of maternal and fetal cardiovascular parameters, progress of labor, Apgar scores, acid-base status, and the NACS, we conclude that addition of 1:300,000 epinephrine to bupivacaine during lumbar epidural anesthesia in the healthy parturient does

Table 5. Percentage of Infants Who Scored 2 for Each Test Item of the Neurologic and Adaptive Capacity Score After Epidural Analgesia Using Bupivacaine With (Group I), and Without Epinephrine (Group II)

	15 Min		2 Hr		24 Hr	
	Group I	Group II	Group I	Group II	Group I	Group II
Adaptive capacity						
Sound	58	36	91	67	92	73
Habituation to sound	67	43	73	64	83	73
Light	83	100	100	100	83	91
Habituation to light	83	79	91	100	100	82
Consolability	100	93	100	92	100	100
Passive tone						
Scarf sign	100	71	100	100	100	100
Elbow Recoil	100	71	100	100	100	100
Lower Limb Recoil	92	86	100	92	92	100
Popliteal Angle	83	93	100	100	100	100
Active tone						
Neck flexors	75	43	91	77	83	91
Neck extensors	83	57	100	75	92	91
Palmar traction	33	64	27	46	75	60
Supporting reaction	83	86	100	83	92	91
Primary reflexes						
Palmar grasp	75	79	36	62	42	73
Automatic walking	58	29	64	54	58	60
Sucking	92	100	91	100	100	100
Moro response	100	100	91	100	92	100
General assessment						
Alertness	100	100	91	100	92	100
Crying	100	79	100	100	100	100
Motor activity	100	100	100	100	100	100
% of good scores on all tests	75	54	100	85	92	82

No significant differences between groups by  $\chi^2$  test.

not prolong labor or adversely affect maternal or neonatal well-being; and that it decreases the incidence of maternal hypotension while prolonging the duration of anesthesia. Further work may be needed to determine whether these results are applicable to high-risk patients with impaired uteroplacental blood flow.

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## Monoamine Oxidase Inhibitors: Should They Be Discontinued Preoperatively?

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EL-GANZOURI AR, IVANKOVICH AD, BRAVERMAN B, MCCARTHY R. Monoamine oxidase inhibitors: should they be discontinued preoperatively? *Anesth Analg* 1985;64:592-6.

*Adverse cardiovascular responses to anesthesia during either electroconvulsive therapy (ECT) or elective surgical procedures were evaluated in 27 patients maintained on chronic (3 months-3 yr) monoamine oxidase inhibitor (MAOI) therapy. Changes in blood pressure and heart rate in study patients (n = 22 ECTs in 13 patients) undergoing ECT were not significantly different from those observed in pa-*

*tients having ECT without prior treatment with MAOIs (n = 45 ECTs in 45 patients). In both groups, blood pressure and heart rate increased significantly after ECT, but returned to baseline levels within 15 min. No complications attributable to MAOIs were observed in study patients (n = 14) undergoing elective surgical procedures. We conclude that discontinuing chronic MAOI therapy prior to anesthesia and surgery is not necessary.*

**Key Words:** ATARACTICS—MAO inhibitors. ANESTHESIA—electroshock.

Monoamine oxidase (MAO) is a general term for a group of intramitochondrial enzymes distributed widely throughout the body. One type of MAO is intraneuronal MAO that is responsible for the deactivation of certain biologically active amines including norepinephrine, 5-hydroxytryptamine, and dopamine (1). Monoamine oxidase inhibitors (MAOIs) increase intraneuronal neurotransmitter pools by inhibiting MAO. Depolarization of these cells results in an increased amount of neurotransmitter being released into the synaptic cleft, thereby increasing postsynaptic depolarization and adrenergic stimulation. MAOIs are currently being used in the treatment of severe depression. The maximal inhibition of MAO by the MAOIs is achieved within a few days, even though their behavioral antidepressant effect may not be observed for 2-3 weeks.

The current recommendation is that MAOIs be discontinued 2 weeks prior to anesthesia because of the potential for serious adverse drug interactions (2-4). Reports of adverse responses in patients taking MAOIs include hypertension, hypotension, hyperpyrexia, hyperreflexia, convulsions, and hepatotoxicity (5,6).

However, no controlled prospective evaluations of the risks involved in anesthesia practice in patients chronically treated with MAOIs have been reported. The purpose of this study was to observe cardiovascular responses and adverse reactions to a variety of anesthetic, ECT, and surgical procedures in these patients.

### Methods

Twenty-seven patients, 15 females and 12 males, between the ages of 23 and 84 volunteered to participate in the study and gave informed consent. This study was reviewed and approved by the Human Investigation Committee of Rush Presbyterian-St. Luke's Medical Center. All patients were on chronic MAOI therapy and were scheduled for either electroconvulsive therapy (ECT) (group I) or elective surgical procedures (group II).

The first group ( $n = 13$ ) received 0.4 mg of atropine intravenously prior to induction of anesthesia. ECTs were often performed more than once in the same patient and thus a total of 22 ECTs were performed in these 13 patients; each procedure was considered an independent event. Anesthesia was induced with thiopental, 1-3 mg/kg, and muscle relaxation was achieved with succinylcholine, 0.5-1.0 mg/kg intravenously. Heart rate, blood pressure, and body (axillary) temperature were recorded prior to, 1 min after,

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Table 1. Patients on MAOI Inhibitors Undergoing Surgical Procedures

Operation	MAOI drug	Duration of MAOI drug	Anesthetic technique	Postoperative pain relief	Comments
Exploratory laparotomy	Tranlycypromine 30 mg/day	7 months	Thiopental, succinylcholine, N <sub>2</sub> O-O <sub>2</sub> , enflurane, and pancuronium	Morphine	No adverse reactions; uneventful recovery
Tibial osteotomy	Tranlycypromine 30 mg/day	1 year	Thiopental, N <sub>2</sub> O-O <sub>2</sub> , halothane	Morphine	"
Lipoma of thigh	Tranlycypromine 20 mg/day	4 months	Thiopental, succinylcholine, N <sub>2</sub> O-O <sub>2</sub> -halothane	Morphine	"
Cystoscopy × 2	Tranlycypromine 30 mg/day	3 years	Thiopental, N <sub>2</sub> O-O <sub>2</sub> , diazepam, fentanyl	Fentanyl	"
Excision of popliteal cyst	Tranlycypromine 30 mg/day	2 years	Etomidate, succinylcholine, N <sub>2</sub> O-O <sub>2</sub> -enflurane	Fentanyl	"
Removal of tibial plate	Tranlycypromine 20 mg/day	3 years	Spinal tetracaine 1% 12 mg	Morphine	"
Vaginal hysterectomy	Tranlycypromine 20 mg/day	1 year	Thiopental, succinylcholine, N <sub>2</sub> O-O <sub>2</sub> , isoflurane	Morphine	"
Total gastrectomy	Phenelzine 45 mg/day	8 months	Thoracic epidural anesthesia, 13 ml, bupivacaine 0.5%, and thiopental, succinylcholine, N <sub>2</sub> O-O <sub>2</sub> , isoflurane	Continuous epidural morphine	Intraoperative hypotension treated by phenylephrine
Total knee replacement	Tranlycypromine 45 mg/day	3 months	Thiopental, succinylcholine, N <sub>2</sub> O-O <sub>2</sub> -halothane	Morphine	No adverse reactions; uneventful recovery
Laparoscopy, exploratory laparotomy	Tranlycypromine 75 mg/day	1 year	Thiopental, succinylcholine, N <sub>2</sub> O-O <sub>2</sub> , halothane and pancuronium	Morphine	"
Lumbar laminectomy	Tranlycypromine 30 mg/day	2 years	Etomidate, succinylcholine, N <sub>2</sub> O-O <sub>2</sub> , isoflurane, and fentanyl 0.25 mg	Morphine	"
Transurethral resection of prostate	Tranlycypromine 30 mg/day	3 years	Spinal anesthesia 10 mg tetracaine 1%	Morphine	"
Dilatation and curettage of the uterus	Isocarboxazid 30 mg/day	4 months	Etomidate, diazepam, fentanyl	—	"
Cataract extraction	Pargyline 10 mg/day	3 years	Intravenous sedation and analgesia by diazepam and fentanyl	Fentanyl	"

and 15 min after ECT. The data were compared to a control group of patients having ECTs with identical premedication and anesthesia, but not taking MAOIs ( $n = 45$  ECTs in 45 patients).

The second group ( $n = 14$ ) (Table 1) received oral

diazepam, 10–15 mg, 2 hr preoperatively. Anesthesia was induced with 1–3 mg/kg thiopental intravenously ( $n = 8$ ) or etomidate 0.3–0.6 mg/kg ( $n = 3$ ). If indicated, their tracheas were intubated, facilitated by succinylcholine administration, 1.0–1.5 mg/kg intra-

Table 2. Responses During ECT With (MAOI) and Without (C) Chronic MAOI Treatment<sup>a</sup>

	Before ECT		After ECT			
	C <sup>b</sup>	MAOI <sup>c</sup>	1 min		15 min	
			C	MAOI	C	MAOI
Blood pressure						
Systolic	133 ± 4	129 ± 4	162 ± 5	149 ± 4	139 ± 4	131 ± 6
Diastolic	77 ± 2	77 ± 3	97 ± 3	93 ± 4	83 ± 3	84 ± 4
Mean	96 ± 3	94 ± 3	118 ± 3	112 ± 4	101 ± 3	100 ± 4
Heart rate	83 ± 2	84 ± 2	99 ± 2	102 ± 5	88 ± 2	84 ± 3
Body temperature	97.6 ± 0.1	97.9 ± 0.2	97.1 ± 0.1	98.0 ± 0.3	97.3 ± 0.3	97.6 ± 3

<sup>a</sup>Mean ± SEM. <sup>b</sup>n, 45 treatments in 45 patients. <sup>c</sup>n, 22 treatments in 13 patients.

venously. Anesthesia was maintained with halothane/N<sub>2</sub>O (*n* = 4), enflurane/N<sub>2</sub>O (*n* = 2) or isoflurane/N<sub>2</sub>O (*n* = 3). Additionally, four patients had intravenous fentanyl, 0.05–0.25 mg anesthesia, two had spinal anesthesia, and one patient had thoracic epidural 0.5% bupivacaine anesthesia. One patient received epidural morphine 0.2 mg/hr during surgery and throughout the postoperative period. Twelve of the fourteen patients in group II received fentanyl or morphine intravenously for postoperative analgesia. The following were monitored from the preanesthetic period through postanesthetic recovery: blood pressure (direct or indirect), electrocardiogram, skin and core temperatures, and the degree of neuromuscular blockade.

The statistical significance of intra- and inter-group differences in changes in blood pressure, heart rate, and body temperature were compared between group I and the control group and were evaluated by analysis of variance. Differences were considered statistically significant at the *P* < 0.05 level of probability. In group II patients, overall significant variations in response to anesthetic management were recorded.

## Results

### Group 1

Systolic, diastolic, mean blood pressures, and heart rates increased significantly 1 min after ECT in both the control group and the MAOI group (Table 2). The changes in mean blood pressure and heart rate from pre-ECT to 1 min post-ECT were not significantly different from the control group. In both groups blood pressure and heart rate returned to baseline values within 15 min. No significant changes were observed in body temperature. Additionally, no unusual clinical observations were made in patients in the study or control groups.

### Group 2

Thirteen of the 14 patients undergoing elective surgery (Table 1) had no adverse reactions at any time during the perioperative period. The eighth patient had a brief episode of hypotension that responded to treatment with lactated Ringer's and phenylephrine (three divided doses of 0.1 mg intravenously). No adverse hemodynamic or psychological responses were noted postoperatively.

## Discussion

Although many concerns have been expressed in the anesthetic literature about anesthetic management of patients on MAOI therapy (3,7), only a few published reports justify these concerns (5,6,8). Most reports of adverse effects have been related to MAOI overdose (1). A significant number of published cases ascribe adverse reactions to the "cheese effect" (9). This effect is attributed to the inhibition of liver monoamine oxidase that allows increases in plasma concentrations of tyramine, an amino acid present in a variety of foodstuffs that possesses indirect-acting sympathomimetic properties. Other indirect-acting sympathomimetic drugs have been reported to produce adverse reactions as well (10–12).

The literature on drug interactions during anesthesia in patients on MAOIs is limited. Potentiation and prolongation of the effects of meperidine, morphine, pentazocine, pentobarbital, amylbarbital, and thiopental have been reported (4,13,14). The mechanism of such interactions has been ascribed to decreased 5-hydroxytryptamine metabolism and inhibition of narcotic metabolism in the liver. However, a study examining the effects of narcotics in 15 volunteers who had been receiving an MAOI for 3–8 weeks found that all subjects reacted normally to intramuscular injections of meperidine and morphine (15). As we have demonstrated in the present study,



other investigators have shown no adverse responses in patients receiving chronic MAOI therapy undergoing narcotic anesthesia (16,17).

Chronic antidepressant therapy can be associated with diminished postsynaptic, central,  $\beta$ -adrenergic receptor activity (18-20). Down-regulation in the limbic system and other cerebral structures, measured by cyclic-AMP generation, has been demonstrated to occur over 7-21 days in chronic animal studies using MAOIs and tricyclic antidepressants (TCAs) (21-23). Similar investigations of TCAs have demonstrated a more complex chronic response for cerebral  $\alpha$ -adrenergic and peripheral  $\alpha$ - and  $\beta$ -adrenergic receptors. Menkes et al. (25,26), for example, found enhanced central  $\alpha_1$ -adrenergic receptor responses in rats as a result of increased receptor affinity after chronic TCA treatment. Responses of  $\beta_1$ -adrenergic receptors have not been found to be altered by TCAs, but cardiac adrenergic nerves released more norepinephrine after stimulation, presumably from decreased  $\alpha_2$ -presynaptic inhibition (22,24). Thus TCAs and possibly MAOIs appear to induce reciprocal changes in central  $\alpha_1$ - and  $\beta$ -adrenergic receptors (26), but have little effect on peripheral  $\beta_1$  responsiveness. The chronic effects of TCAs and MAOIs on peripheral  $\alpha_1$ -adrenergic receptors has not been well defined.

Acute treatment (8-15 days) with TCAs in dogs results in an increased arrhythmogenicity in response to various adrenergic challenges (27,28) but chronic treatment (6 weeks) failed to alter arrhythmogenicity or adrenergic responsiveness (29). Acute (8-14 days) treatment with MAOI and TCA in dogs followed by challenges with volatile anesthetics and epinephrine is associated with increases in arrhythmogenicity that are similar with both types of drugs (28). Our own initial studies (30) have demonstrated increased responses of heart rate and blood pressure to ephedrine and norepinephrine in dogs anesthetized with enflurane/fentanyl/ $N_2O$  after 2 weeks of treatment with MAOI, but the responses returned to normal by the third week of treatment.

Extrapolation from these animal studies suggests that patients on chronic MAOI therapy would not be adversely affected during anesthesia or by adrenergic challenges. A similar lack of adverse responses to adrenergic challenges has been observed in patients on chronic TCA therapy (31). Studies with MAOIs and TCAs suggest that this may be a result of adaptations occurring during chronic antidepressant therapy.

In summary, a group of 27 patients on chronic (greater than 3 weeks) MAOI therapy was found to have no adverse responses in the perioperative period while receiving anesthesia for ECT or elective surgical procedures. We did not evaluate patients who had

recently (less than one month) begun MAOI therapy. These later patients may be potentially at a higher risk before adaptation has occurred, and more work is needed to determine the potential for adverse responses in this group. Furthermore, we did not evaluate indirect-acting sympathomimetic amines or meperidine because of the number of previously reported adverse interactions with these agents. More studies in animals and volunteers are needed in this area, but, based upon our findings and those of other investigators, as well as an understanding of the neuropharmacology involved with chronic antidepressant therapy, we believe that discontinuation of chronic MAOI therapy prior to surgery is not necessary.

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## Fentanyl and Alfentanil Suppress Brainstem Pain Transmission

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YUGE O, KITAHATA LM, COLLINS JG, MATSUMOTO M, TABATABAI M, SUZUKAWA M, TANAKA A. Fentanyl and alfentanil suppress brainstem pain transmission. *Anesth Analg* 1985;64:597-600.

*The effects of intravenously administered fentanyl (25  $\mu$ g/kg,  $n = 9$ ; 50  $\mu$ g/kg,  $n = 5$ ) and alfentanil (12.5  $\mu$ g/kg,  $n = 5$ ; 25  $\mu$ g/kg,  $n = 7$ ) on the noxiously evoked, single-unit activity of cells in the nucleus reticularis gigantocellularis (NRGC) were studied in decerebrate cats. Only cells of the NRGC excited exclusively by supramaximal electrical stimulation of A delta fibers (noxious stimulation) of the superficial radial nerve were studied. The noxiously evoked*

*activity of all cells in the NRGC was suppressed by the administration of opioids (by 58 and 88% for fentanyl, 25  $\mu$ g/kg and 50  $\mu$ g/kg, respectively; by 35 and 78% for alfentanil 12.5  $\mu$ g/kg and 25  $\mu$ g/kg, respectively). Fentanyl and alfentanil effects were antagonized by the intravenous administration of naloxone. These results indicate that opioid suppression of noxiously evoked activity is seen in neurons located in the brainstem, and thus suppression of brainstem neurons may be important in the production of fentanyl and alfentanil analgesia.*

**Key Words:** ANALGESICS—fentanyl, alfentanil. BRAIN—evoked responses.

For many years, opioid analgesia was assumed to result from an undefined drug action in the brain, which depressed pain signals and modified the affective component of pain. The discovery of endogenous opiate systems, including opiate receptors in many parts of the body, offered the possibility that opioid analgesia may result from specific drug actions at anatomically defined sites. A likely candidate for the site of such drug action is the nucleus reticularis gigantocellularis (NRGC), which is located at the caudal end of the reticular formation. The NRGC has been described as an important site for the afferent transmission of pain information and as having a role in the relaying of descending information to the spinal cord (1). The cells in NRGC have been reported to be activated when noxious stimuli were presented to their peripheral receptive fields (2). Increased activity of the NRGC neurons has also been associated with increased escape behavior in trained animals (3,4). While the NRGC neurons respond to several types of peripheral stimuli (5,6), it is agreed that many NRGC

neurons respond exclusively or maximally to noxious stimulation of peripheral receptive fields.

The newer opioids are of particular interest pharmacologically because of their greater potency and different pharmacokinetics. For example, alfentanil is a short-acting drug because of its rapid plasma clearance and small volume of distribution (7). Future use of these newer opioids requires an increased understanding of their sites and mechanisms of action in the production of analgesia. Because previous studies demonstrated that both anesthetic and analgesic drugs are capable of suppressing noxiously evoked activity in the NRGC (8-11), this present study was carried out in order to determine whether the newer opioids have similar effects on pain transmission in the NRGC.

### Methods

All institutional, state, and Federal guidelines for the care and use of laboratory animals were followed during all aspects of this study. Twenty-six cats of either sex, weighing from 2-4 kg, were used. Under halothane-nitrous oxide-oxygen anesthesia, a tracheotomy was performed, and a femoral artery and vein were cannulated for direct arterial blood pressure recording and intravenous fluid and drug administration. After placement in a Horsley-Clark stereotaxic apparatus, electrolytic lesions were made in the mid-

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brain reticular formation in order to render the animals decerebrate. Decerebration allowed discontinuation of general anesthesia, thus permitting the drug studies to be carried out in unconscious anesthetic-free preparations. Animals received an infusion of lactated Ringer's solution, which contained 0.1% galamine triethiodide ( $4-8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ). The lungs were ventilated with pure oxygen using a volume-cycled ventilator connected to a non-rebreathing system. End tidal  $\text{CO}_2$  was maintained between 4 and 5%. Systolic arterial blood pressure was maintained above 100 torr by the administration of lactated Ringer's solution, as necessary. Rectal temperature was maintained at  $37 \pm 1^\circ\text{C}$ . A bilateral pneumothorax was produced in order to reduce movement of the brainstem due to respiration.

The superficial radial nerve was exposed and prepared for the placement of two pairs of silver bipolar electrodes: the proximal pair for stimulating and the distal pair for recording compound action potentials. Paraffin film was placed beneath the nerve and electrode in order to shield them from the surrounding tissue. A paraffin oil pool was made around the nerve at each electrode in order to protect it from cooling and drying. The temperature of the paraffin oil was maintained at  $37 \pm 0.5^\circ\text{C}$  by a thermostatically controlled heating apparatus. Before searching for the NRGC neurons, the threshold intensity and the intensity required for maximum activation of A beta and A delta components of the compound action potential of the superficial radial nerve were determined. These intensities were determined so that it would be possible to distinguish the NRGC neurons that respond to A beta fiber stimulation, as well as A delta fiber stimulation from those NRGC neurons that respond exclusively to supramaximal intensities necessary for A delta fiber stimulation. To facilitate microelectrode penetration to the NRGC, the snout of the animal was tilted downward  $30^\circ$  from the horizontal plane. After occipital craniotomy, a tungsten microelectrode with a 1-2 micron exposed tip (impedance 9-14  $\text{M}\Omega$  at 1000 Hz) was inserted from 1.0-2.5 mm rostral and lateral to the obex at a depth of 2000-5000 microns from the dorsal surface. The electrode was inserted at an angle of  $25^\circ$  from the vertical plane by a hydraulic micromanipulator.

Supramaximal activation of A delta fibers was used to evaluate the response characteristics of each single NRGC cell. As the microelectrode was advanced into the area of the NRGC, the contralateral superficial radial nerve was electrically stimulated. The stimulation consisted of 100-msec pulse trains (100 Hz, 1-msec duration). In previous studies, these stimulus parameters were found to be optimal for the activation

of the NRGC neurons. Only cells that respond exclusively to A delta fiber stimulation were studied. During recording of neuronal activity of the NRGC neurons, the electrical stimulus was repeated every 60 sec at twice the maximal voltage required for activation of A delta fibers.

The drug studies were performed on only one neuron in each animal to eliminate the accumulation of drug effects. Extracellularly recorded single-neuron activity was amplified by a differential AC amplifier, displayed on a cathode ray oscilloscope, and with the use of amplitude discrimination recorded on magnetic tape. Data were recorded and analyzed off line on a digital computer (DEC PDP 11/40). After a 10-30 min control period during which time the evoked activity following superficial radial nerve stimulation was averaged in order to provide control data (Fig. 1), fentanyl (25 or 50  $\mu\text{g}/\text{kg}$ ) or alfentanil (12.5 or 25  $\mu\text{g}/\text{kg}$ ) was administered intravenously over a period of 3 min (each animal received only one dose of one drug). After administration of the drug, stimulus-evoked activity was recorded every 60 sec and monitored continuously for a minimum of 30 min. Thirty minutes after fentanyl administration, naloxone, 0.1 mg, was administered intravenously in order to evaluate the reversal of the fentanyl effect. An additional 0.1 mg of naloxone was administered 35 min after the 50  $\mu\text{g}/\text{kg}$  dose of fentanyl. Owing to the rapid recovery after alfentanil administration, the effects of naloxone on alfentanil were not evaluated.

Analysis of the data included the comparison of mean evoked activity during control situations with mean evoked activity elicited after drug administration. Evoked activity was considered to be any increase in neuronal firing frequency greater than the mean baseline spontaneous rate. The statistical significance of the data was assessed by paired *t*-test for

Figure 1. Polygraph tracing of a control study. The top traces represent the activity of a single neuron in the NRGC, which was activated by A delta fiber stimulation of the superficial radial nerve, as indicated at the arrows. Neuronal activity is expressed as impulses/sec. In this control study, the A delta stimulation caused this cell to fire at a rate of 102 impulses/sec, 104 impulses/sec, 106 impulses/sec, and 98 impulses/sec. A beta stimulation (the third arrow) did not cause significant activation of this neuron.

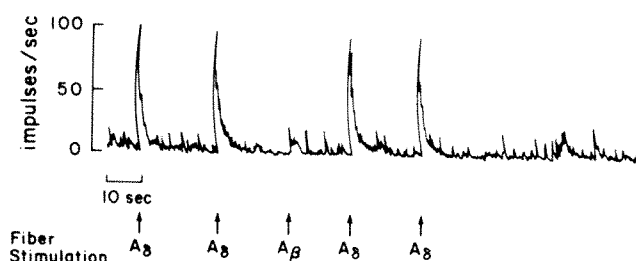
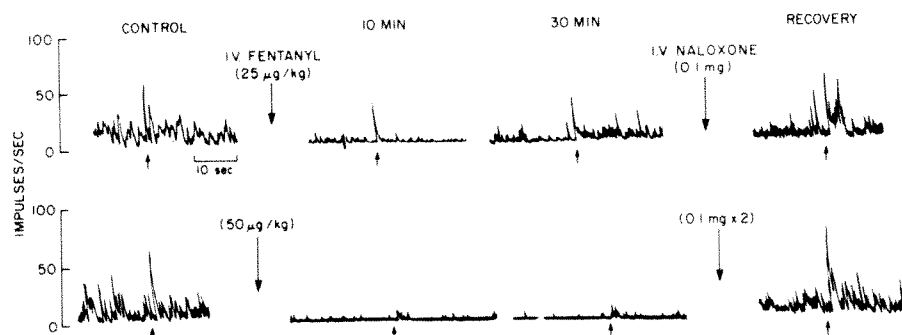




Figure 2. Fentanyl suppression of two different cells located in the NRG and the reversal of that suppression by naloxone. In the control period, A delta stimulation, as indicated by the arrows, caused activation of these neurons. 10 min after the intravenous administration of 25  $\mu\text{g}/\text{kg}$  or 50  $\mu\text{g}/\text{kg}$  of fentanyl, the evoked activity had been reduced to 56% and 8% of control values, respectively. Fentanyl-induced suppression was still clearly evident 30 min after its administration. Subsequent administration of 0.1 mg or 0.2 mg of naloxone restored the evoked activity to 98% (top trace) and 108% (bottom trace) of the control values.



the changes from control values and unpaired *t*-test for the differences between dosages. Adequate recording conditions could not be maintained for all cells for the duration of each study. Therefore, the number of cells included in the analysis decreases with time.

## Results

### Fentanyl

The effects of fentanyl were studied in 14 cells. Figure 2 demonstrates the typical fentanyl suppression of noxiously evoked activity of two different NRG neurons and the reversal of that suppression by naloxone. The effects of 25 and 50  $\mu\text{g}/\text{kg}$  of fentanyl on the mean noxiously evoked activity of all the neurons studied is shown in Figure 3. Note the rapid suppression of the noxiously evoked activity, the duration of suppression up to 30 min, and the rapid reversal of that suppression after the intravenous administration of 0.1 mg of naloxone. The maximum suppression produced by 50  $\mu\text{g}/\text{kg}$  was significantly greater than the maximum suppression produced by 25  $\mu\text{g}/\text{kg}$ .

### Alfentanil

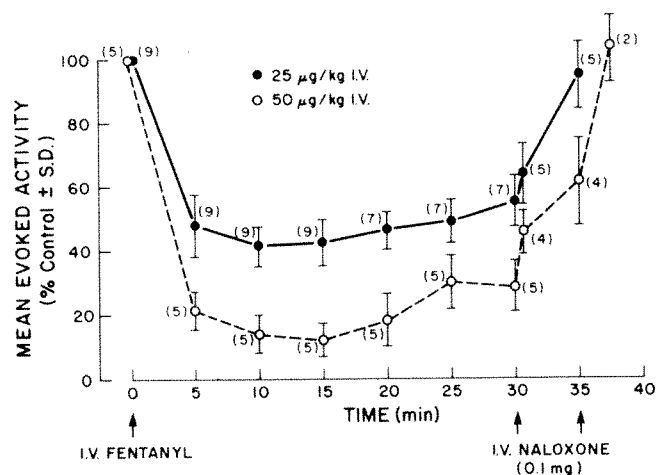
Figure 4 shows the effects of alfentanil (12.5 and 25  $\mu\text{g}/\text{kg}$ ) on the mean noxiously evoked activity of the neurons studied after its administration. Both doses of alfentanil were capable of producing a significant suppression that occurred rapidly. In contrast to the fentanyl data, however, the recovery from suppression after alfentanil was so rapid that within 15 min after the administration of 12.5  $\mu\text{g}/\text{kg}$ , the mean noxiously evoked activity had returned to within 20% of control values. Twenty-five  $\mu\text{g}/\text{kg}$  of alfentanil produced a greater suppression of noxiously evoked activity than did 12.5  $\mu\text{g}/\text{kg}$ . A comparison of Figures 3 and 4 reveals that although 25  $\mu\text{g}/\text{kg}$  of alfentanil

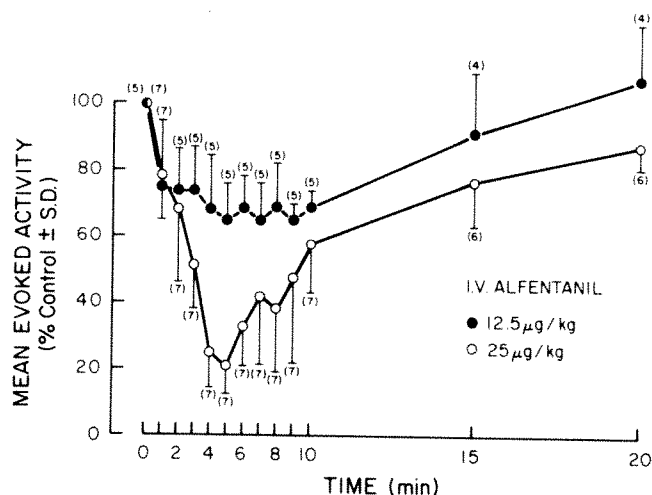
produced almost as great a degree of suppression as did 50  $\mu\text{g}/\text{kg}$  of fentanyl, the duration of that maximal depression by alfentanil was very short, and the recovery from alfentanil was much more rapid. Twenty minutes after the administration of 25  $\mu\text{g}/\text{kg}$  of alfentanil, the mean evoked activity had returned to within 10% of control values.

## Discussion

There is increasing evidence that opiates are capable of selectively depressing neuronal activity at many

Figure 3. This figure shows the effects of intravenously administered fentanyl, 25  $\mu\text{g}/\text{kg}$  (solid line) and 50  $\mu\text{g}/\text{kg}$  (dashed line), on the mean evoked activity of all cells studied. The abscissa represents time, the ordinate mean evoked activity expressed as percent of control. The bars indicate  $\pm 1$  SD. Numbers in parentheses indicate the number of cells studied at each point. Significant suppression began within 5 min after drug administration. Maximal suppression was 58% at 10 min after 25  $\mu\text{g}/\text{kg}$ , and 88% at 15 min following 50  $\mu\text{g}/\text{kg}$ . Thirty minutes after drug administration, the intravenous administration of naloxone (0.1 mg) caused significant recovery from maximum suppression. Note that 0.1 mg of naloxone completely reversed the 25  $\mu\text{g}/\text{kg}$  dose but that an additional 0.1 mg of naloxone (administered at 35 min) was required to reverse the 50  $\mu\text{g}/\text{kg}$  dose.





**Figure 4.** This figure shows the effect of intravenously administered alfentanil, 12.5 µg/kg and 25 µg/kg, on the mean evoked activity of all the cells studied. The abscissa represents time, the ordinate mean evoked activity expressed as percent of control. The bars indicate  $\pm 1$  SD. The numbers indicate the number of cells studied at each point. Significant suppression ( $P < 0.05$ ) began within 1 min after drug administration. Maximal suppression was 35% 5 min after the administration of 12.5 µg/kg and 78% 5 min after 25 µg/kg. Note the rapid recovery from suppression seen after both doses of alfentanil, such that within 20 min after drug administration, activity had returned to control levels. Compare this with lack of recovery for a period of 30 min after fentanyl administration, as shown in Fig. 3.

sites within the central nervous system. Reports that the NRGC may be important to the signaling of pain (1,2), and that the noxiously evoked activity of the NRGC neurons can be inhibited by anesthetic and analgesic drugs (8-11), suggest that suppression of noxiously evoked activity of the NRGC neurons may be important to the overall production of analgesia. Behaviorally, Takagi (12) reported that morphine or enkephalin, when microinjected into the NRGC, produced a dose-related, naloxone reversible analgesia in a tail-pinch test. Thus it seems possible that opiate suppression of the noxiously evoked activity of the NRGC neurons may be associated with the production of analgesia.

The results of the present study indicate that the administration of two potent new opioids can suppress the noxiously evoked activity of the neurons located in the NRGC. The drugs are capable of producing a significant suppression of noxiously evoked activity that, for fentanyl, is of fairly long duration and is reversible by naloxone. Of particular interest was the duration of action after the administration of alfentanil. In keeping with the known pharmacokinetics of the drug (7), the duration of action of alfentanil was much shorter than that of fentanyl. However, suppression by alfentanil was almost as profound

as that after the administration of fentanyl. The ability of alfentanil to produce this degree of suppression would not be predicted from the known analgesic potencies of the two drugs. (In animals, alfentanil is three to four times less potent than fentanyl (13).) It must be remembered that although we know that drug-induced suppression of known neuronal systems is associated with analgesia, we do not know what degree of suppression is associated with a given level of analgesia. The greater than expected degree of suppression seen in this study may reflect a local differential effect.

These results indicate that the newer opioids are capable of suppressing noxiously evoked activity of NRGC neurons located in the midbrain reticular formation. This new information identifies additional sites and possible mechanisms of action whereby opioid analgesia is produced.

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## Verapamil Is Not a Therapeutic Adjunct to Dantrolene in Porcine Malignant Hyperthermia

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Gerald A. Gronert, MD

GALLANT EM, FOLDES FF, REMPEL WE, GRONERT GA. Verapamil is not a therapeutic adjunct to dantrolene in malignant hyperthermia. *Anesth Analg* 1985;64:601-6.

*We have investigated the hypothesis that the calcium antagonist verapamil might be useful for prevention or treatment of malignant hyperthermia (MH) in MH-susceptible (MHS) swine. MH episodes were triggered in four groups of four swine with halothane alone or combined with succinylcholine (SCh) and, with and without verapamil. MH episodes were reversed by therapy with dantrolene and NaHCO<sub>3</sub> in all groups. Verapamil did not alter MH episodes triggered by halothane alone or combined with SCh. The dantrolene-NaHCO<sub>3</sub> requirements for reversal of MH*

*were greater for the groups receiving halothane-SCh, but did not differ in groups pretreated with and without verapamil. In vitro verapamil (25  $\mu$ M) did not reduce responses of intact muscle fibers to halothane and, in fact, exaggerated some halothane-induced responses. High concentrations of verapamil (0.5 mM) caused contractures in MHS but not in normal muscles. Neither our in vivo nor in vitro results support the use of verapamil in the treatment of MH. Further, doses of dantrolene used to reverse these MH episodes, although admittedly small (1-2 mg/kg), did not produce myocardial depression when used in combination with verapamil.*

**Key Words:** HYPERTHERMIA—malignant. PHARMACOLOGY—verapamil.

In recent years verapamil and other calcium channel blockers (calcium antagonists) have been employed in the treatment of cardiovascular disorders (1,2). The therapeutic effects of verapamil have been attributed to the inhibition of the slow calcium current in cardiac and vascular smooth muscle (3,4). Slow calcium channels of skeletal muscle are also blocked by verapamil (5), and in vitro contractions of both directly (6,7) and indirectly (6) stimulated rodent skeletal muscles are inhibited by micromolar concentrations of verapamil. That lower concentrations of verapamil were required for reducing tension with direct, rather than with indirect stimulation (6), indicates that the primary site

of the inhibitory effect of verapamil is probably postsynaptic (6). Because extracellular calcium is not essential for skeletal muscle contraction (8-10), it is most likely that the inhibitory effect of verapamil is due to its ability to block the sodium and potassium channels of the sarcolemma (11-14). The inhibitory effect of verapamil on contraction is not antagonized by increased extracellular calcium (6,7,15). In rat muscle, concentrations of verapamil that did not decrease muscle contraction enhanced the inhibitory effect of dantrolene sodium both in vitro (16) and in vivo (17).

It has been suggested that malignant hyperthermia (MH) is caused by abnormal entry of extracellular calcium into skeletal muscle fibers (18) and that it might therefore be treated with verapamil (19,20). It has also been suggested (6) that doses of verapamil that have no adverse cardiovascular effects may increase the therapeutic efficacy of dantrolene, the agent of choice for the prevention and treatment of MH emergencies (21). Decreasing the therapeutic dose of dantrolene by verapamil conceivably could have two beneficial effects: it might influence favorably the tachyarrhythmia encountered in MH emergencies and it might reduce the large volume of dantrolene solution (3-10 ml/kg) required for the arrest of the MH crisis in humans.

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In the present study we investigated the following: a) the effect of the preliminary administration of verapamil on the triggering of MH by halothane or halothane plus succinylcholine chloride (SCh) in MH-susceptible (MHS) swine; b) the influence of verapamil on the dose of dantrolene required for the reversal of the MH reaction; and c) the *in vitro* effects of verapamil and verapamil plus halothane on normal and MHS porcine muscle.

## Materials and Methods

### *In Vivo Experiments*

The *in vivo* experiments were carried out on 16 purebred Pietrain pigs, which developed hindlimb rigidity, indicating MH-susceptibility, within 2.5 min when inhaling 3% halothane by mask. At least five days after testing, definitive studies were performed. The animals ( $30.7 \pm 1.5$  (SEM) kg weight) were anesthetized with 15 to 20 mg/kg intravenous thiopental, intubated and ventilated with N<sub>2</sub>O–O<sub>2</sub> using a constant volume ventilator (Harvard pump). Minute volume of ventilation and N<sub>2</sub>O/O<sub>2</sub> ratio were adjusted to maintain the PaO<sub>2</sub> between 125 and 200 mm Hg and a PaCO<sub>2</sub> of  $40 \pm 1$  mm Hg. Ventilatory parameters were kept constant throughout the experiment so that any alteration of PaCO<sub>2</sub> could be assumed to reflect changes in CO<sub>2</sub> production.

Pilot studies revealed that, even when administered over a 30-min period during the inhalation of 1% halothane in N<sub>2</sub>O–O<sub>2</sub>, 0.8–1.0 mg/kg of verapamil caused severe bradycardia and hypotension. No adverse cardiovascular effects were observed when 0.3 mg/kg verapamil was administered intravenously over 2 min and infused thereafter at the rate of  $0.01 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  throughout the experiment. Consequently, verapamil was administered according to the latter schedule throughout this study, during exposure to MH triggering and to therapeutic drugs.

Eight pigs received verapamil. Thirty minutes after the start of verapamil infusion, four were challenged with 1% halothane and four others with 1% halothane and 3 mg/kg succinylcholine chloride (SCh) administered 15 min after the start of the inhalation of halothane. This part of the protocol examined the effect of verapamil in modifying the onset of MH. Eight other pigs did not receive verapamil pretreatment. Four were challenged with halothane and four others with halothane and SCh. After MH occurred, all 16 pigs were treated with dantrolene and NaHCO<sub>3</sub>. Thus the groups, four pigs each, were halothane-triggered with and without preceding infusion of verapamil, or

halothane–SCh-triggered with and without a preceding infusion of verapamil. This part of the protocol examined the effect of verapamil in modifying the treatment of MH with dantrolene.

When PaCO<sub>2</sub> exceeded 65 mm Hg, indicating the triggering of MH, the administration of halothane and N<sub>2</sub>O was discontinued and the animals were hyper-ventilated with O<sub>2</sub>. At the same time NaHCO<sub>3</sub> (weight  $\times 0.3 \times$  negative BEa mEq) and 1 mg/kg dantrolene were injected intravenously. If the metabolic responses were not controlled adequately by these measures within 5 min, additional increments of dantrolene 0.5 mg/kg and NaHCO<sub>3</sub> were injected until PaCO<sub>2</sub>, pHa, and BEa returned to control levels.

Because no marked changes of esophageal temperature occurred in the course of the experiments, cooling was not necessary. When the animals awakened, they were extubated, returned to their pens, and evaluated again the next morning.

### *In Vitro Experiments*

Studies were conducted on bundles of intact muscle cells dissected from a small forelimb muscle of normal and MHS pigs (22). Muscles were removed from pigs under thiopental–N<sub>2</sub>O anesthesia before administration of halothane or other drugs. To facilitate oxygenation, muscles were subdivided into bundles of cells that were intact from tendon-to-tendon and had cross-sectional diameters of approximately  $1 \times 2$  mm or less. Experiments were conducted at 37°C in porcine physiological saline solution (135 mM NaCl, 4 mM KCl, 2.35 mM CaCl<sub>2</sub>, 1 mM NaH<sub>2</sub>PO<sub>4</sub>, 0.85 mM MgCl<sub>2</sub>, 12 mM NaHCO<sub>3</sub>, 5.5 mM glucose) aerated with 5% CO<sub>2</sub>–95% O<sub>2</sub>.

For mechanical studies, muscle bundles were mounted horizontally in a tissue bath between platinum plate electrodes that extended the length of the muscle and stimulated with supramaximal DC pulses. Continuous twitches were elicited by single 1-msec stimuli at 0.05 Hz and tetani with 0.3-sec trains of 1-msec square pulses at 200 Hz. Control responses were recorded at the end of a 30-min equilibration period. Muscles were then exposed either to 25  $\mu\text{M}$  verapamil for 15 min, or to 25  $\mu\text{M}$  verapamil for 15 min and to 2.5% halothane in the ensuing 15 min. Twitch and tetanic tensions were monitored with a Statham UC-2 force displacement transducer and recorded with a Nicolet 2090 digital oscilloscope and a Gould 220 chart recorder.

For electrical measurements, muscle bundles were pinned to the sylgard chamber floor and impaled with 3 M KCl-filled glass microelectrodes. Membrane po-



Table 1. The Influence of Verapamil on MH Triggered by 1% Halothane

Parameter	Before triggering		During MH reaction		After treatment	
	V <sup>a</sup>	C <sup>b</sup>	V	C	V	C
PaO <sub>2</sub> (mm Hg)	152 ± 7	150 ± 7	104 ± 7	106 ± 12	72 ± 1 <sup>c</sup>	65 ± 3 <sup>c</sup>
PaCO <sub>2</sub> (mm Hg)	39 ± 1	40 ± 1	70 ± 2 <sup>c</sup>	68 ± 4 <sup>c</sup>	43 ± 5	46 ± 4
pHa	7.45 ± 0.02	7.43 ± 0.03	7.16 ± 0.02 <sup>c</sup>	7.14 ± 0.03 <sup>c</sup>	7.46 ± 0.01	7.48 ± 0.03
BEa (mEq/L)	0.5 ± 1.7	0.8 ± 2	-8 ± 0.5 <sup>c</sup>	-9 ± 2 <sup>c</sup>	3 ± 2	7 ± 2 <sup>c</sup>
BP (mm Hg) <sup>d</sup>	120 ± 7	106 ± 7	72 ± 4 <sup>c</sup>	67 ± 4 <sup>c</sup>	—	—
HR (beats/min)	171 ± 4	150 ± 9	128 ± 9	116 ± 12	—	—

*n* = 4, each group. Values given as mean ± SEM.

<sup>a</sup>V: verapamil 0.3 mg·kg<sup>-1</sup> and 0.01 mg·kg<sup>-1</sup>·min<sup>-1</sup> infused for 30 min before and during MH; and as treatment, 1 mg·kg<sup>-1</sup> dantrolene and NaHCO<sub>3</sub> 82 ± 20 mEq.

<sup>b</sup>C: control without verapamil; treatment with dantrolene 1 mg·kg<sup>-1</sup> and NaHCO<sub>3</sub> 95 ± 10 mEq.

<sup>c</sup>FiO<sub>2</sub> = 0.2.

<sup>d</sup>Mean intraarterial BP.

<sup>e</sup>Significantly different from "before triggering" (*P* < 0.05).

Table 2. The Influence of Verapamil on MH Triggered by 1% Halothane and 3 mg·kg<sup>-1</sup> Succinylcholine

Parameter	Before triggering		During MH reaction		After treatment	
	V <sup>a</sup>	C <sup>b</sup>	V	C	V	C
PaO <sub>2</sub> (mm Hg)	146 ± 7	14 ± 7	80 ± 3	89 ± 4	73 ± 3 <sup>c</sup>	70 ± 11 <sup>c</sup>
PaCO <sub>2</sub> (mm Hg)	39 ± 0.5	39 ± 0.4	84 ± 4 <sup>c</sup>	87 ± 7 <sup>c</sup>	41 ± 3	53 ± 6
pHa	7.45 ± 0.02	7.47 ± 0.02	7.01 ± 0.06 <sup>c</sup>	7.05 ± 0.05 <sup>c</sup>	7.49 ± 0.02	7.50 ± 0.03
BEa (mEq/L)	1 ± 2	-0.5 ± 2	-14 ± 3 <sup>c</sup>	-10 ± 2 <sup>c</sup>	5 ± 3	12 ± 1 <sup>c</sup>
BP (mm Hg) <sup>d</sup>	120 ± 6	108 ± 7	70 ± 6 <sup>c</sup>	58 ± 1 <sup>c</sup>	—	—
HR (beats/min)	155 ± 13	159 ± 16	175 ± 41	191 ± 9	—	—

*n* = 4, each group. Values given as mean ± SEM.

<sup>a</sup>V: verapamil 0.3 mg·kg<sup>-1</sup> and 0.01 mg·kg<sup>-1</sup>·min<sup>-1</sup> infused for 30 min before and during MH; and as treatment, 1.62 ± 0.12 mg·kg<sup>-1</sup> dantrolene and NaHCO<sub>3</sub> 280 ± 29 mEq.

<sup>b</sup>C: control without verapamil; treatment with dantrolene 1.88 ± 0.12 mg·kg<sup>-1</sup> and NaHCO<sub>3</sub> 275 ± 17 mEq.

<sup>c</sup>FiO<sub>2</sub> = 0.2.

<sup>d</sup>Mean intraarterial BP.

<sup>e</sup>Significantly different from "before triggering" (*P* < 0.05).

tentials were recorded by conventional techniques with a WPI 701 microprobe amplifier and a Nicolet 2090 digital oscilloscope.

Data are expressed as mean ± standard error of the mean. Statistical analysis utilized a one-way analysis of variance to detect significant changes within groups; then the Student *t*-test for paired data compared results within groups. Dantrolene and bicarbonate doses between groups were compared using the unpaired *t*-test. *P* < 0.05 was considered significant.

## Results

### *In Vivo Experiments*

Verapamil did not attenuate or exaggerate the MH triggering effect of either halothane alone (Table 1) or halothane and Sch (Table 2). It had no influence on

either the time of onset or the severity of the MH. When precipitated by 1% halothane, the hypermetabolic reaction was reversed equally well after discontinuing halothane by the intravenous injection of 1 mg/kg dantrolene and NaHCO<sub>3</sub> with or without verapamil pretreatment (Table 1). The mild respiratory depression, observed after treatment in the dantrolene alone group, was probably caused by the accidental over-correction of the metabolic acidosis by NaHCO<sub>3</sub> (BEa = 7 ± 1). Doses of dantrolene and NaHCO<sub>3</sub> were not different, i.e., verapamil did not alter therapeutic doses.

When the MH reaction was triggered by halothane + Sch, the amount of both dantrolene and NaHCO<sub>3</sub> required for the termination of the MH reaction was greater than in the groups triggered by halothane alone (Table 2). There were no differences, however, in the dantrolene and NaHCO<sub>3</sub> requirements between the

**Table 3.** The Effects of Verapamil (V) and Halothane (H) on Normal and MHS Porcine Skeletal Muscle, in vitro (mean  $\pm$  SE).

Muscle	Number	Control tetanic tension (kg $\cdot$ cm $^{-2}$ )	Treatment	Tension (as % of control tetanic tension)	
				Twitch	Tetanus
Normal	8	2.6 $\pm$ 0.2	Control	11 $\pm$ 2	100
			15 min V <sup>a</sup>	12 $\pm$ 2	91 $\pm$ 2 <sup>c</sup>
			30 min V plus 15 min H	12 $\pm$ 2	91 $\pm$ 2 <sup>c</sup>
Normal	7	2.5 $\pm$ 0.2	Control	10 $\pm$ 2	100
			15 min H <sup>b</sup>	11 $\pm$ 2	101 $\pm$ 2
			Control	20 $\pm$ 4	100
MHS	7	3.1 $\pm$ 0.2	15 min V	22 $\pm$ 6	88 $\pm$ 2 <sup>c</sup>
			30 min V plus 15 min H	20 $\pm$ 3	60 $\pm$ 7 <sup>c</sup>
			Control	19 $\pm$ 3	100
MHS	6	3.6 $\pm$ 0.2	15 min H	27 $\pm$ 4	84 $\pm$ 3 <sup>c</sup>

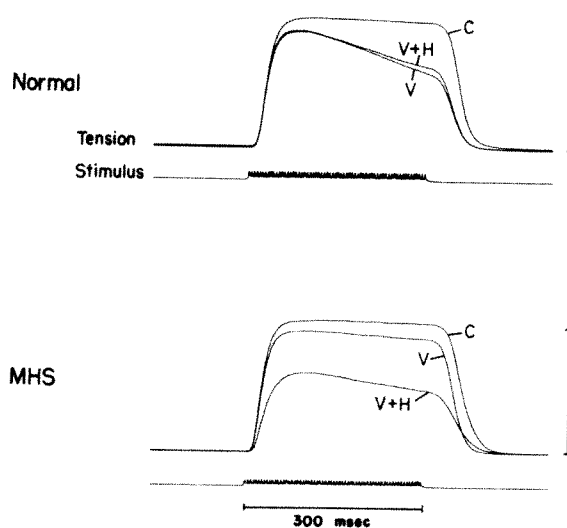
<sup>a</sup>Verapamil concentration, 25  $\mu$ M.<sup>b</sup>Halothane concentration, 2.5% vol/vol in the bath.<sup>c</sup>Significantly different from control ( $P < 0.05$ ).

groups treated with verapamil-dantrolene and dantrolene alone. The BEa was again greater in the group given dantrolene alone than in the group given verapamil-dantrolene, and moderate respiratory depression was present in these animals (BEa =  $12 \pm 1$ ). All pigs survived and appeared normal the next morning.

### *In Vitro Experiments*

The effects of verapamil on isolated bundles of intact muscle cells are shown in Figures 1 and 2 and Table 3. Figure 1 displays individual responses that represent the means given in Table 3. Tetanic tension of MHS muscles was depressed slightly less by verapamil than was that of normal muscles. The effect of halothane on tetanus of MHS muscles was enhanced by verapamil and the combined depression was more than additive (Table 3). In normal muscles, halothane did not depress tetanic tension. When halothane was combined with verapamil there was either no further depression or a slight reversal of the verapamil-induced tetanic depression. Verapamil did not affect the small halothane-induced contracture ( $1.4 \pm 0.3\%$  of control tetanic tension) sometimes observed in MHS muscles. Verapamil (50  $\mu$ M) significantly depolarized the surface membrane by 10 mV in normal pig muscle (from  $-87.0$  to  $-77.0$  mV). The trend in this direction was not significant for MHS muscle (from  $-83.7$  to  $-79.6$  mV).

Very high (500  $\mu$ M) concentrations of verapamil significantly increased twitch tension of both normal and MHS muscle, but caused moderate contracture only in MHS muscle (Fig. 2). The increase of the twitch



**Figure 1.** The effects of 25  $\mu$ M verapamil on tetanic responses of bundles of intact cells from normal and MHS skeletal muscles. Tension records selected were representative of responses included in Table 3. Muscle bundles were stimulated by 300-msec trains of 1-msec DC pulses (18 V/cm) at 200 Hz. Each set shows control (C) response of the muscle, response after 15 min exposure to verapamil (V), and after 15 min further exposure to verapamil in the presence of halothane (V + H). Muscle bundle cross-sectional dimensions were the following: normal— $0.6 \times 1.3$  mm; MHS— $0.7 \times 1.3$  mm. Note that verapamil alone caused a moderate decrease of tetanic tension in MHS muscle that was depressed further by exposure to halothane in the presence of verapamil. In normal muscle the effects of verapamil alone and combined with halothane were similar. Vertical tension calibration bars equal  $3.0$  kg $\cdot$ cm $^{-2}$ .

was sustained in normal muscle, but was followed rapidly by complete block in MHS muscle. Subsequent exposure of normal muscle to 2.5% halothane further increased the twitch and caused moderate (6%) contracture, never observed with verapamil or halo-

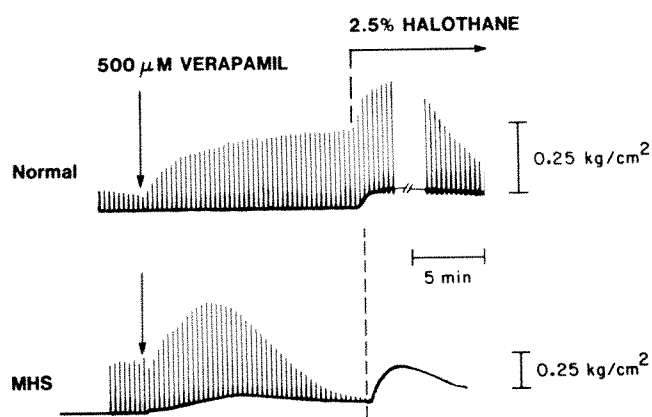


Figure 2. The effects of 500  $\mu$ M verapamil on twitch tension of normal and MHS muscles. Records were selected as representative of those obtained in five experiments. Bundles of intact muscle cells were stimulated at 0.05 Hz with supramaximal 1-msec DC pulses. At the first arrow, 500  $\mu$ M verapamil was added to the bath. At the dashed line, halothane was bubbled through the chamber to achieve a bath concentration of 2.5%. Muscle bundle cross-sectional dimensions were the following: normal— $0.9 \times 1.2$  mm; MHS— $0.65 \times 1.65$  mm. At the break in the upper record, recorder gain was reduced, and this distorted part of the record has been removed for the sake of clarity. Note that 500  $\mu$ M verapamil increased the twitch tension of both normal and MHS muscle. In normal muscle the increase was maintained and augmented by halothane. In MHS muscle the initial increase of twitch tension was followed by complete block. Verapamil alone caused contracture in MHS muscle only. Halothane in the presence of verapamil enhanced this contracture in the MHS muscle and initiated a contracture in the normal muscle.

thane alone. In MHS muscle, halothane had no effect on the verapamil-induced twitch depression, but increased contracture from 1.4 to 14% (of control tetanic tension).

## Discussion

The present study confirms prior results (27), and explores in greater detail the interactions among MH-triggering agents, dantrolene and verapamil, *in vivo*. Additionally, the responses of MHS muscles to verapamil alone and combined with halothane have been studied *in vitro*.

Pretreatment with the highest dose of verapamil that had no adverse circulatory effects did not alter the MH-triggering effect of halothane or SCh and did not change the amount of dantrolene and  $\text{NaHCO}_3$  required for the termination of the MH reaction. The only marginally beneficial effect of verapamil was that BEa was lower in the verapamil-treated groups (see Tables 1 and 2). This difference, however, may have been iatrogenic. Probably because of this, the mild respiratory depression observed in the control groups

receiving dantrolene alone did not develop in the groups receiving verapamil-dantrolene.

There are confusing data concerning myocardial depression by dantrolene: while large doses of dantrolene (7.5 mg/kg) had no adverse cardiovascular effect in MHS pigs (23), still larger (9.9 mg/kg) doses of dantrolene, administered together with 0.1 mg/kg verapamil followed by the continuous infusion of 5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  verapamil, caused severe myocardial depression in normal pigs (24). All of these doses of dantrolene were much higher than those required for the termination of the MH reaction in this study. However, the treatment of human MH occasionally requires total doses of dantrolene similar to those observed to cause myocardial depression in pigs, when used together with verapamil. Because both verapamil and dantrolene have a tendency to accumulate in cardiac muscle (25,26), the concomitant use of these two agents could cause prolonged myocardial depression. Because of this, the combined use of dantrolene and verapamil for the treatment of human MH is not advisable.

Our *in vitro* results also fail to support the rationale for the use of verapamil in treating MH. Verapamil enhanced the halothane-induced depression of tetanic tension in porcine MHS muscle, but failed to block halothane-induced contractures. We have no explanation for the finding that in this study, verapamil had no beneficial effect either *in vivo* or *in vitro*, on the halothane-induced MH reaction, while, in a single human biopsy specimen, it prevented the effect of enflurane on MHS muscle *in vitro* (20).

The lack of any therapeutic effect of verapamil indicates that it is unlikely that entry of extracellular calcium via slow channels plays an important role in the mechanism of MH reaction in MHS pigs or humans. The treatment of choice for MH remains the discontinuation of anesthetic agents, hyperventilation with 100%  $\text{O}_2$ , 2–3 mg/kg dantrolene, 2–4 mEq/kg  $\text{NaHCO}_3$ , and cooling. If necessary, dantrolene may be repeated every 5 min up to a total dose of 10 mg/kg. More  $\text{NaHCO}_3$  should also be administered if the initial dose fails to correct metabolic acidosis. Tachydysrhythmia, if sustained, should be treated by the intravenous injection of procainamide.

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## Statistical Methods in Anesthesia Articles: An Evaluation of Two American Journals during Two Six-Month Periods

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AVRAM MJ, SHANKS CA, DYKES MHM, RONAI AK, STIERS WM. Statistical methods in anesthesia articles: an evaluation of two American journals during two six-month periods. *Anesth Analg* 1985;64:607-11.

*Simple criteria were used to evaluate the statistical analyses in 243 articles from two American anesthesia journals published in the latter six months of 1981 and 1983. Eighty-two percent of the articles reported the use of control measures and 37% reported randomization of treatment, where they were possible. Data were classified as nominal, ordinal, or interval; as independent or related samples; as two-sample or more-than-two-sample cases. The descriptive, inferential, and correlative tests used were evaluated for appropriate application and primary errors were identified. Nine percent of the 722 descriptive statistics had major errors, most of which were a description of ordinal data as though they were interval. The incidence of erroneous applications of 394 in-*

*ferential statistical tests was 78%. Nearly three-quarters of the 308 primary inferential statistical errors involved either use of a test for independent samples on related data (and vice versa) or multiple applications of an uncorrected test to the same data. Only 4% of the 113 statistics of association were considered erroneous, most because the method was not identified. No differences were detected in the incidence of errors in either experimental design or statistical analysis across time or across the two anesthesia journals. Fifteen percent of the 243 articles in both journals at both times were without major errors in statistical analysis. Recognition of potential sources of error should make it easier for investigators to use experimental designs and statistical analyses appropriate to their needs.*

**Key Words:** STATISTICS—medical. PUBLICATIONS—anesthesia journals.

Statisticians who have critically evaluated the biomedical literature have found errors in the use of statistical methods in nearly half the articles sampled (1-7). When journals began to insist upon proper use of appropriate statistical methods, the quality of statistical analysis improved dramatically (3,6). According to Glantz (7) most mistakes in statistical methods are simple errors in experimental design or in the use of elementary hypothesis tests, errors that bias the results in favor of the treatment. The purpose of the present study was to assess the experimental design and statistical analysis used in articles appearing in two American anesthesia journals with an interval of two years. The articles were assessed by applying simple criteria found in standard sources (1,7-11).

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### Materials and Methods

We evaluated the experimental designs and statistical analyses of the scientific articles appearing in *Anesthesia and Analgesia* during July to December 1981 and during July to December 1983 (the second halves of Volumes 60 and 62, respectively) and comparable articles appearing in *Anesthesiology* during the same six-month periods (Volumes 55 and 59, respectively). The journals were reviewed by the calendar month of their publication. Lists of the titles of the articles from the two journals in the same month of both years were combined and the order in which they were to be read was assigned by a random number generator. After independent assessment by each of the present authors, the articles for each month were reviewed by all of the authors, in the same random order, to obtain a consensus evaluation. No attempt was made to determine the effect of inappropriate design or analysis on the conclusions reached in the paper being evaluated.

The experimental design of each article was evaluated first. If a control group (1) or randomization of treatment (8) was possible, their presence or absence

was noted and the types of control and methods of randomization were identified. Other inadequacies in the experimental design, such as too small a number of subjects studied, though very important (12), were not considered, because they were beyond the scope of the present study.

The data reported in the articles were classified as nominal, ordinal, or interval according to the criteria of Siegel (9) (Table 1), as independent or related samples (7,9,10), and as a two-sample or a multiple-sample (>2) case (7,9). The descriptive, inferential, and correlative tests (Table 2) were then judged appropriate or inappropriate based on Altman et al. (10), Glantz (7), Siegel (9), and Wallenstein et al. (11). Descriptive statistical errors included failure of the article to identify the descriptive statistics used, the use of interval descriptive statistics for ordinal data, and the use of the standard error of the mean rather than the standard deviation to describe data dispersion (6,13). Although noted during review, the use of the standard error was not considered a major problem because of the ease of conversion to the standard deviation. Errors in inferential statistical analysis were noted when the statistical tests were unidentified, when parametric tests were used on ordinal data, when the numbers in the cells of the contingency table were inadequate for  $\chi^2$  analysis, or when tests for independent samples were used on related data and vice versa. Further assessment of inferential statistical analysis considered the presence (when required) and appropriateness of tests used after an analysis of variance (ANOVA post hoc tests) as well as multiple applications of an uncorrected test to the same data. The effect of skewed data or inhomogeneity of variance on the appropriateness of a statistical analysis of interval data was not considered; it was often difficult to detect these in summarized data and some analyses are robust enough to accommodate these to some degree (10). The errors in correlation analysis were failure to specify the test used and regression analysis of mean data.

In any one manuscript the application of a statistical test to a level of measurement was counted singly, no matter how often this application was repeated. For any given test in any article only the primary errors are reported. These were the first errors encountered in the chronologic order of performing the test. As an example, if serial blood pressures were measured in the same individuals and multiple comparisons with the baseline pressures were made using unpaired *t*-tests, the primary error was considered to be the application to related data of a test for independent samples, even though the error of multiple applications of a test to the same data without correction was also made.

Table 1. Definition of the Three Levels of Measurement (9)

Level of measurement <sup>a</sup>	Examples	Operations on data
Nominal—all-or-none data	Arrhythmias present/absent Alive/dead	Equivalence
Ordinal—data are ordered by magnitude using a relative scale or category	ASA physical status Apgar score	Ranking
Interval—data are from a range of continuous values on a scale of known constant intervals	°C Weight	Arithmetic

<sup>a</sup>Data collected at a high level of measurement (interval > ordinal > nominal) may be converted to and treated as though of a lower level of measurement.

The observed frequencies of errors in either experimental design or statistical analysis for both journals at both times were compared with the expected frequencies using a two-by-two-by-two [(time 1/time 2)  $\times$  (journal 1/journal 2)  $\times$  (error/no error)]  $\chi^2$  test statistic with the Yates correction for continuity (14). The criterion for rejection of the null hypothesis was  $P < 0.05$ .

## Results

When the experimental designs of the 243 manuscripts from the two six-month periods of both journals were compared, there were no differences demonstrated with respect to the actual or potential use of either control measures ( $P > 0.05$ ) or randomization ( $P > 0.05$ ) (Table 3). Eighteen percent of the articles reviewed had unsatisfactory or no controls (when they were possible) and half of these were considered unsatisfactory because the controls were historical. Randomization of treatment was reported in 37% of the articles where it was possible, but the actual method of randomization (random number table or Latin square experimental design) was reported in only one-tenth of these.

There were 722 descriptive statistics including the 498 listed in Table 2, 175 uses of the standard error of the mean, and 40 reports of the raw data. The index of central tendency was almost exclusively the mean, while nearly half of the descriptions of data dispersion were the standard error of the mean. The most common major error in the use of descriptive statistics was the description of ordinal data as though it were

Table 2. Incidence of Statistics Quoted<sup>a</sup> in the Two Six-Month Periods Studied (7,9)

Level of measurement	Descriptive statistics	Inferential statistics				Statistics of association between variables
		Two-sample case		>2-sample case		
		Related samples	Independent samples	Related samples	Independent samples	
Nominal	Mode (2) Cumulative frequency (66)	McNemar test (0)	Fisher exact probability test (7) $\chi^2$ test (29)	Cochran Q-test (0)	$\chi^2$ test for >2 independent samples (4)	Contingency coefficient (0)
Ordinal	Median (8) Frequency distribution (20)	Wilcoxon signed-rank test (8)	Mann-Whitney U-test (12) Wilcoxon rank sum (11) Kolmogorov-Smirnov two-sample test (2)	Friedman two-way ANOVA (0)	Kruskal-Wallis one-way ANOVA (3)	Spearman rank correlation coefficient (4)
Interval <sup>a</sup>	Mean (265) Standard deviation (104) Range (33)	Paired <i>t</i> -test (65) Repeated measures one-way ANOVA (16)	Unpaired <i>t</i> -test (87) One-way ANOVA (93)	Repeated measures two-way ANOVA (1)	Two-way ANOVA (8)	Linear regression and Pearson product-moment correlation coefficient (84)

<sup>a</sup>Of the statistics not reported in this classification there were 224 descriptive, 48 inferential, and 25 associative statistics. See text for details.

<sup>b</sup>ANOVA post hoc tests comparing means include the Bonferroni *t*-tests (11), Duncan's test (7), Dunnett's test (2), Neuman-Keuls test (14), Scheffe's test (6), and Tukey's test (6). Fifty-seven post hoc tests are not listed; see text for details.

Table 3. Use of Control and Randomization in the Two Six-Month Periods Studied

	<i>Anesthesia and Analgesia</i> Vol. 60, 1981	<i>Anesthesiology</i> Vol. 55, 1981	<i>Anesthesia and Analgesia</i> Vol. 62, 1983	<i>Anesthesiology</i> Vol. 59, 1983	Total
Number of manuscripts	55	67	64	57	243
Satisfactory control	38	47	45	41	171
Unsatisfactory or no control <sup>a</sup>	6(2 <sup>b</sup> )	14(8 <sup>b</sup> )	9(4 <sup>b</sup> )	9(5 <sup>b</sup> )	38(19 <sup>b</sup> )
Randomization reported	14(10 <sup>c</sup> )	9(9 <sup>c</sup> )	23(22 <sup>c</sup> )	14(13 <sup>c</sup> )	60(54 <sup>c</sup> )
Randomization possible, not used <sup>d</sup>	22	32	25	25	104

<sup>a</sup>In an additional 34 articles the study design precluded the use or inclusion of a control group.

<sup>b</sup>Historical controls.

<sup>c</sup>The method of randomization was not stated.

<sup>d</sup>Randomization was not possible in an additional 79 articles.

interval (Table 4). The total incidence of major errors in descriptive statistics was 9%; there were no differences detected between the two journals ( $P > 0.05$ ).

Table 2 lists 346 of the 394 inferential statistical tests identified. The unpaired and paired *t*-tests represented 39% of the 394 inferential statistical tests used and the independent samples and repeated measures one-way analysis of variance (ANOVA) accounted for 28%. All nonparametric tests, on the other hand, accounted for only 19% of the 394 inferential statistical tests used and 38% of these were the  $\chi^2$  test for two

independent samples. The tests not listed in Table 2 include 17 unidentified tests, 12 instances of analysis of covariance (ANCOVA), and 7 other types of ANOVA (e.g., multivariate ANOVA, split plot ANOVA).

Follow-up tests for ANOVA were not included in the total number of tests because they were considered to be an integral part of the ANOVA, after its detection of a difference. Forty-six of the 103 post hoc tests that use the *F*-test or the Studentized range are listed in the footnote of Table 2. The post hoc tests not listed include 23 that were either unspecified (9)

Table 4. Origins of Primary Descriptive Statistical Errors in the Two Six-Month Periods Studied

	<i>Anesthesia and Analgesia</i> Vol. 60, 1981	<i>Anesthesiology</i> Vol. 55, 1981	<i>Anesthesia and Analgesia</i> Vol. 62, 1983	<i>Anesthesiology</i> Vol. 59, 1983	Total
Method not described	3	2	0	0	5
Ordinal data, interval description	17	12	18	13	60
Standard error of the mean <sup>a</sup>	31	49	42	35	157

<sup>a</sup>Not included as a major error due to its ease of conversion to the standard deviation

Table 5. Origins of Primary Inferential Statistical Errors in the Two Six-Month Periods Studied

	<i>Anesthesia and Analgesia</i> Vol. 60, 1981	<i>Anesthesiology</i> Vol. 55, 1981	<i>Anesthesia and Analgesia</i> Vol. 62, 1983	<i>Anesthesiology</i> Vol. 59, 1983	Total
Unidentified test	7	0	4	6	17
Ordinal data, interval test	7	5	5	7	24
Inadequate numbers for $\chi^2$	6	1	9	4	20
Related data, independent test (and vice versa)	17	24	26	22	89
Inappropriate follow-up to variance analysis	6	6	7	5	24
Multiple applications of an uncorrected test	29	38	36	31	134

or not used when they were required (14), and 27 unpaired (18) and paired (9) *t*-tests that were not corrected for multiple applications.

The origins of the 308 primary inferential statistical errors in the two six-month periods of both journals are listed in Table 5. Approximately one-quarter of the errors in inferential statistical tests were due to the following: failure to identify the test used; application of an interval test to ordinal data; inadequate numbers for  $\chi^2$  analysis; and inappropriate or no follow-up to variance analysis. The most common sources of primary statistical errors in the articles reviewed were the application of a test for independent samples to related data (and vice versa), which accounted for more than one-quarter of the primary errors, and multiple applications of an uncorrected test to the same data, which accounted for nearly half of the errors. The error rate in applying the 315 parametric inferential statistical tests was 83%, while that for the 79 nonparametric tests was 61% (Table 6). The incidence of erroneous application of the 394 inferential statistical tests in the two six-month periods studied in both journals was 78% and there was no difference detected between the journals ( $P > 0.05$ ).

The statistics of association between variables for 88 of the 113 instances identified are listed in Table 2. Other such tests include 11 nonlinear least squares regressions and 4 unspecified tests. Linear regression and Pearson product-moment correlation coefficient represented 74% of the 113 statistics of association.

There were five (4%) primary errors in the application of statistics of association, four because the tests used were not described, and one because of linear regression analysis of mean data. The incidence of errors detected in statistics of association was too small for further analysis.

The percentage of articles that contained no errors in statistical analysis (other than errors involving use of the standard error of the mean) were 9% in the latter half of Volume 60 and 16% in the latter half of Volume 62 of *Anesthesia and Analgesia*, and 18% in Volume 55 and 16% in Volume 59 of *Anesthesiology*. Fifteen percent of the 243 articles in both journals at both times were without errors.

## Discussion

This study, using only simple criteria, found a high incidence of error in experimental design and statistical analysis in both American anesthesia journals evaluated in both six-month periods. This substantiates the concern expressed in a recent editorial (15) about the weakness of statistical techniques in the biomedical sciences in general, and anesthesia in particular. The lack of difference across time indicates that it may be too early for the level of statistical sophistication in the anesthesia literature to change as a result of the editorial (15). The error rate would be drastically reduced by greater attention to two fundamental issues: the differences between indepen-



Table 6. Errors in Applying Inferential Statistical Tests in the Two Six-Month Periods Studied

	<i>Anesthesia and Analgesia</i> Vol. 60, 1981	<i>Anesthesiology</i> Vol. 55, 1981	<i>Anesthesia and Analgesia</i> Vol. 62, 1983	<i>Anesthesiology</i> Vol. 59, 1983	Total
Number of manuscripts	55	67	64	57	243
Both <i>t</i> -tests	36 of 40	37 of 41	34 of 42	20 of 30	127 of 153
All ANOVA and ANCOVA	18 of 19	27 of 33	35 of 40	34 of 45	114 of 137
Other parametric tests	8 of 8	0 of 1	5 of 8	6 of 8	19 of 25
All parametric tests	62 of 67	64 of 75	74 of 90	60 of 83	260 of 315
All nonparametric tests	10 of 20	10 of 15	13 of 21	15 of 23	48 of 79
All parametric and nonparametric tests	72 of 87	74 of 90	87 of 111	75 of 106	308 of 394

dent-samples vs related-samples tests, and the differences between two-sample vs greater than two-sample tests. There are readily available tests appropriate for independent or paired data and for two-sample vs more than two-sample data (Table 2). These methods do not require sophisticated statistical skills, nor are they likely to "strangle" anesthesiology literature (16).

Feinstein's survey of the statistical procedures used in six leading medical journals found that the vast majority of these were elementary procedures: *t*-tests,  $\chi^2$  test, standard deviation, or standard error of the mean (17). These findings were repeated in a review of articles in the *New England Journal of Medicine* (18) and in the present study (Table 2). This study (Tables 3-6) supports the observation by Glantz (7) that most errors in statistical analysis involve the misuse of elementary hypothesis tests, the lack of a control, or failure to randomize treatments. Thus, while the concerns voiced by Stanley and Pace (16) are not unreasonable, the present results suggest that improvement in statistical analysis would be achieved if experimental design and the type of data collected were given appropriate attention (7-11,14,19). Such guidelines provide a foundation for the use, with understanding, of statistical software packages for microcomputers (20). The optimal solution, of course, is to have a statistician included in the research team from the beginning.

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## Special Article

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# Anesthetic Implications of Prolonged QT Interval Syndromes

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The prolonged QT interval syndromes are one of a number of rare abnormalities that may profoundly influence anesthetic management. They are not well known and their incidence has not yet been fully established, but due to an increased awareness of the syndromes, they are now being recognized more often. The syndromes occur in a congenital form (LQTS), of which over 500 cases have been described (1), and an acquired form (ALQTS), the causes of which are many. This article describes the prolonged QT interval syndromes and outlines their anesthetic management.

### Description of the QT Interval

The prolonged QT syndromes are characterized by an increase of the QT interval (QTI) corrected for heart rate (QT<sub>c</sub>) using Bazett's formula (2):

$$QT_c = \frac{QTI}{\sqrt{R-R \text{ interval}}}$$

The QTI extends from the beginning of the QRS complex to the end of the T wave, and electrically represents both depolarization and repolarization of the ventricles (3). Mechanical systole in patients with LQTS is normal (4). The period of repolarization appears to be the more important in the genesis of the prolonged QT interval. The QTI varies with age, sex, and heart rate. Its measurement is difficult on account of the indeterminate end point of the T wave. It is also important to rule out a bundle branch block, as this will produce a prolonged QT<sub>c</sub> due to a widened qRs. The QTI is most accurately measured in an ECG lead with an initial q before the QRS complex, and where there is a distinct T wave. As a rule of thumb, the QTI

should not exceed half of the R-R interval (5). The upper limit of normal of the QT<sub>c</sub> is 0.44 sec (1).

### The Congenital Long QT Interval Syndrome

There are two distinct types of the prolonged QTI: a congenital form, which is discussed here, and an acquired form, which is discussed later. The causes, presentation, and management of the two types are different. There are four forms of LQTS:

- 1) Cardioauditory syndrome was first described by Jervell and Lange-Neilsen in 1957 (6). This condition, also known as the surdocardiac syndrome, consists of a prolonged QT<sub>c</sub>, congenital neural deafness, and syncopal attacks or sudden death (7). The syncopal attacks coincide with ventricular tachycardia, fibrillation (8,9), or asystole that may result in sudden death (7). The cardioauditory syndrome is inherited as an autosomal recessive trait (9).
- 2) Romano et al. (10) and Ward (11) described a similar syndrome without hearing loss. This is inherited as an autosomal dominant trait (11-13) and is three times more frequent than the form associated with deafness (14).
- 3) Familial ventricular tachycardia described by von Bernuth et al. (15) is a further variant of LQTS, in which the QTI is normal at rest but increases with exercise. The prolongation of the QTI is an essential feature of the syndrome, but it may vary in degree from patient to patient, and in the same patient. It is inherited as an autosomal dominant trait (16).
- 4) A sporadic variety is implied by a number of case reports in which there is no family history, thus indicating that spontaneous mutations resulting in a prolonged QT<sub>c</sub> may also occur (1,17-21). It has features similar to any one of the above three types.

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### *Clinical Features of LQTS*

The patient usually presents at a young age with a history of syncope. A family history of congenital deafness and sudden death is often present (15). Consanguinity of parents predisposes to LQTS (9). Deafness occurs in 30% of patients with LQTS, and between 0.25–1% of patients with congenital deafness have LQTS (14,22). The deafness is of the perceptive type with some preservation of low tones, and is due to atrophy of the organ of corti and spinal ganglion (22). The frequency of syncopal attacks varies from once or twice per week, to once or twice in a lifetime (7,14). The condition may simulate epilepsy, anginal, or Stokes–Adams attacks (7). The attacks usually occur less frequently with aging (7,14).

Patients with LQTS may also have minor attacks with nonspecific symptoms that include a “sensation of butterflies,” numbness, disorientation, anxiety, moans or crying, sweating, palpitations, angina, fullness of the chest, and acute abdominal discomfort (7,17,23–25). Quite commonly the child will stop moving or lie down (4). The attacks are mainly due to transient ventricular tachycardia, fibrillation, or asystole (7), but any form of dysrhythmia may occur (25). Syncopal attacks are precipitated by adrenergic stimuli or sympathetic nervous system discharges, especially those associated with exercise, excitement, fatigue, and fright (6,14,22,26). The mechanisms responsible for these dysrhythmias include impulses that reach depolarized ventricles, producing a ventricular tachycardia (12); extrasystoles producing an R on T phenomenon (12); an increase in blood pressure resulting in pressure-induced ventricular extrasystoles due to subendocardial ischemia (12); and different QT intervals (of which only the longest is recorded on the ECG) occurring simultaneously within the ventricles, i.e., an asymmetry of QT intervals (27). Apart from deafness that may be present, physical examination of these patients is usually normal.

### *The Electrocardiograph*

The diagnostic feature is a prolonged QT<sub>c</sub> that may be evident only after exercise. Heart rate is usually normal, although a bradycardia may be present (4,15,28). Sinus rhythm is present, but episodes of atrial flutter (8), bigeminy (29), premature ventricular contractions (29) (unifocal or multifocal), or torsades de pointes (14,30) occur. T waves are often abnormal; being prominent, broad, biphasic, or altering in polarity (7,14). P waves may be superimposed on the T waves (12). U waves can be present (31).

### *Pathogenesis*

The basic abnormality of LQTS is undecided. At present the most accepted theory is that LQTS results from an asymmetrical adrenergic stimulus in the heart (14,18). This is supported by the facts that syncopal attacks are usually triggered by events known to increase sympathetic activity, the characteristic electrocardiographic signs of LQTS can be reproduced by asymmetrical stimulation of sympathetic tone (32), and the best therapeutic results are obtained by antagonizing sympathetic activity, i.e.,  $\beta$ -adrenergic blockers or ganglionectomy (14). The level of this autonomic imbalance is not known, but may be within the brainstem (33), the sympathetic chain, or the adrenergic nerve terminals (16). The imbalance may be due to decreased activity of the right cardiac sympathetic nerves, or an increased activity of the left (14). The former is more likely because the right cardiac nerves have a predominantly chronotropic effect, whereas the left have mainly an inotropic effect (32,34). However, individual variability occurs, and LQTS may occasionally result from increased activity of the right sympathetic nerves, or a decreased activity of the left (14). The result of the altered sympathetic tone is a delayed repolarization of the ventricles (producing a prolonged QT<sub>I</sub>) that increases the susceptibility of the heart to dysrhythmias (32,35). Exercise, which often initiates the dysrhythmias, exaggerates the imbalance in adrenergic discharge, further increasing the QT<sub>c</sub> in patients with LQTS (14). The high incidence of slow heart rates associated with LQTS (14), and the ability of atropine to shorten the QT<sub>I</sub> in LQTS (6), may imply an abnormality in vagal tone or an imbalance in sympathetic tone in patients with LQTS (14).

Another mechanism proposed to be responsible for LQTS is an abnormality of the blood supply to the sinus node (22). In two of five cases of LQTS that came to autopsy there was marked narrowing of the sinus node artery and focal areas of infarction within the sinus node (22). This may result in abnormal sinus pacemaker function with intermittent failure, allowing the genesis of escape rhythms (22). It is, however, uncertain whether these changes within the sinus node are primary or secondary to the syncopal attacks that occur in LQTS.

In the same autopsies it was also noted that the Purkinje fibers were sparse and lacked the perinuclear clear zone (22). These changes may support a metabolic cause of LQTS, probably related to glycogen metabolism (22). This would possibly explain the association of an eighth cranial nerve palsy with altered myocardial conduction. However, the Purkinje fibers in humans are not important in cardiac repolarization

that produces the prolonged QTI in LQTS (22). Jervell et al. also proposed that an inborn enzymatic deficiency that alters membrane permeability is responsible for LQTS (4). A high association of iron deficiency anemia with the cardioauditory syndrome may also indicate a primary metabolic cause of LQTS (22).

### *Prognosis and Treatment*

The prognosis in untreated patients with LQTS is poor, with a mortality rate of up to 73% (14). This syndrome is also an important cause of sudden death at an early age (7).

Treatment of patients with LQTS is essential in view of the high mortality. This is especially true during the perioperative period when factors precipitating dysrhythmias are common.

*Drugs.* The best drugs for therapy of LQTS are  $\beta$ -adrenergic blockers, which have decreased the mortality from 73 to 6% (14). The exact mechanism by which  $\beta$ -adrenergic blockers act to decrease the incidence of dysrhythmias in LQTS has not yet been established. The  $\beta$ -adrenergic blockers shorten the QTI and the QT<sub>c</sub> in LQTS (in contrast to their effect in normal patients in whom they lengthen the QT<sub>c</sub>) (36). The value of  $\beta$ -adrenergic blockers in LQTS may also be due to their blocking of sympathetic activity, or to their ability to increase the threshold for ventricular fibrillation (37). For adequate treatment it is essential that complete  $\beta$ -adrenergic blockade be achieved. This can be assessed by ECG where the heart rate and QTI decrease, serum propranolol levels, or the patient's response to the Valsalva maneuver during which there should be no change in QTI (38). However  $\beta$ -adrenergic blockers must be used with caution in patients who have a bradycardia, but generally patients with LQTS seem to tolerate high doses of  $\beta$ -adrenergic blockers (14). If a bradycardia should develop it can be treated by adding L-hyoscyamine (14) or by electrical pacing (39).

Phenytoin shortens the QT<sub>c</sub> (25,40) and may be effective in the treatment of LQTS due to its action on the midbrain (25), its ability to decrease synaptic transmission in the stellate ganglion (41), or by its antidysrhythmic effect (25).

Phenytoin is indicated when the dose of a  $\beta$ -adrenergic blocker needs to be reduced due to side effects (14), and therefore has been used as an alternative during pregnancy (16). However phenytoin may cause vitamin K deficiency or a harelip in the neonate (42). Phenytoin has also been used successfully in a

case resistant to  $\beta$ -adrenergic blockers (24). It serves as a second line drug for this condition.

Phenobarbital, though it has no direct effect on the QT<sub>c</sub> (25) may, in conjunction with other drugs, be of value due to a central action (28) or its membrane stabilizing property (43).

Primidone shortens the QTI, has a suppressive action on ventricular dysrhythmias (44), and has been used successfully to treat patients with LQTS (44). The antidysrhythmic action of the antiepileptic agents mentioned above is an advantageous side effect as LQTS is often misdiagnosed as epilepsy (17).

Digoxin shortens the QTI in patients with LQTS, but has no effect on the syncopal attacks (4,8,12,45). Favorable results have only been obtained using a combination of digoxin and a  $\beta$ -adrenergic blocker (14).

Reports on the clinical use of calcium entry blockers in patients with LQTS have been limited to date, but theoretically they may be of value in the treatment of the LQTS due to their antidysrhythmic action. In the case described by von Bernuth et al., a beneficial effect was obtained with all three of the  $\beta$ -adrenergic blockers used, but the best results were obtained with a combination of practolol and verapamil (15).

Encouraging results have been reported with bretylium in the treatment of patients with LQTS (1).

The use of lidocaine is limited to the acute attacks of ventricular dysrhythmias. Although lidocaine prolongs the QTI, it has been successful for the treatment of acute dysrhythmias in LQTS (16,24,45).

*Left stellate ganglion block.* The aim of a left stellate ganglion block in the treatment of patients with LQTS is to temporarily abolish the sympathetic imbalance that exists between left and right cardiac nerves (33). The block also shortens the QTI and raises the threshold for ventricular fibrillation (14). However, blockade of the cardiac nerves may be difficult, and the appearance of a Horner's syndrome is not necessarily an indication of a successful block of the left cardiac nerve (14,23). In addition, dysrhythmias may be precipitated by attempts at performing the block in highly anxious patients, as well as by stimulation of the ganglion by the needle (23). A successful block is best indicated by shortening of the QT<sub>c</sub> on ECG. The main indication for a left stellate block is failure of pharmacological control of the syndrome (14). The action of a stellate ganglion block is only transient, and therefore it is used only to control an acute attack (23), to assess whether a ganglionectomy will be successful, and as emergency preoperative preparation of patients, not on medical treatment, when the anes-



thetist is the first person to diagnose LQTS. In some cases a right stellate ganglion block, rather than a left, will shorten the QTI (14).

**Surgical.** Surgical treatment of LQTS consists of excision of both the left stellate and first three or four thoracic ganglions, thereby ensuring division of the left cardiac sympathetic nerves (14). The indication for a ganglionectomy is failure of medical therapy (14). This form of treatment has been successful in preventing syncope even though the QTI was shortened in only 40% of cases (1). If a right sympathectomy is indicated, which is rare, it is advisable to perform a bilateral sympathectomy in order to prevent left dominance that may be dangerous (14).

**Pacemaker.** A pacemaker is indicated in patients with concomitant conduction defects, (especially a symptomatic bradycardia due to  $\beta$ -adrenergic blockade) (39). Incremental ventricular pacing shortens the QTI (36). Pacing may however induce ventricular fibrillation (21).

In summary, the therapeutic approach to a patient presenting with LQTS is to start with a  $\beta$ -adrenergic blocker. If the patient is unresponsive then phenytoin, primidone, a calcium entry blocker, or bretylium may be added or substituted. If there is no response to medical therapy, a left stellate ganglion block should be done to identify patients who are likely to respond to surgical ablation, which is then undertaken if the block has been successful (Table 1).

### Anesthetic Management of LQTS Before Surgery

Surgery may be necessary either for ganglionectomy needed to treat LQTS or for unrelated procedures. The successful management of patients with LQTS undergoing anesthesia and surgery depends on recognition of the syndrome and prevention of excessive sympathetic nervous system discharge. Patients not diagnosed preoperatively tend to develop life-threatening dysrhythmias during anesthesia (24,46-48). Children with deafness, epilepsy, or a family history of sudden death must have a preoperative electrocardiograph (7,29). Adequate time and effort must be spent in explaining the procedure to deaf patients. The patient's weight should be obtained in order to calculate intraoperative ventilatory and fluid requirements. A hypnotic the night before surgery is advisable.

The patients must be fully  $\beta$ -adrenergic blocked, and should be given their usual dose of  $\beta$ -adrenergic blockers on the morning of surgery. From the anesthetic literature it appears that there may be two

Table 1. Preoperative Treatment of LQTS

$\beta$ -Adrenergic blocker	
↓	
Phenytoin Calcium entry blocker (verapamil) Bretylium Primidone Phenobarbital	} Added or substituted
↓	
Stellate ganglion block	
↓	
Surgery	

subgroups of the LQTS as determined by the response to  $\beta$ -adrenergic blockers and the subsequent anesthetic course: first, those patients who respond to  $\beta$ -adrenergic blockade and have uneventful anesthesia (16,46,48,49); second, those patients not responsive to  $\beta$ -adrenergic blockers and who are on other forms of drug therapy. The latter may develop serious dysrhythmias when anesthetized (29,50). Patients with LQTS who have no history of syncopal attacks nor a family history of sudden death are, in general, at lower risk of developing life-threatening dysrhythmias (31). There have been 10 cases of LQTS reported in the anesthetic literature, 8 cases with the Romano-Ward variety (24,29,46-51), one case of Jervell-Lange-Nielsen (52), and one case of familial ventricular tachycardia (16). Dysrhythmias during the perioperative period have so far only occurred in patients with the Romano-Ward syndrome. Thus it has also been suggested that patients with Romano-Ward syndrome are at greater risk of developing dysrhythmias during anesthesia (52).

The aim of premedication is a calm, placid, and well-sedated patient. Morphine and diazepam make a useful combination. Atropine has been used as part of the premedication (50), but because of the uninhibited sympathetic activity resulting from its vagal blocking effect, it is best avoided (14,29,48). Stellate ganglion block is reserved for those patients who are not adequately controlled on  $\beta$ -adrenergic blockers preoperatively. Any underlying electrolyte imbalance must be corrected.

A quiet and tranquil atmosphere must be present in the operating room, which must also be equipped with adequate monitoring facilities including an ECG, temperature probe, a method for measuring blood loss, and a means to monitor for air embolism if surgery is a ganglionectomy. A defibrillator, transvenous

pacemaker, and the necessary drugs for treating cardiac dysrhythmias should be immediately available.

### *During Surgery*

Here again the emphasis is on prevention of excessive sympathetic stimulation and those factors, including drugs, that may further prolong the QTI. Thus control of anesthesia must be superb. Light anesthesia, hypertension, tachycardia, bradycardia, hypoxemia, and hypo- or hypercarbia must be avoided. Hypothermia prolongs the QTI, and therefore the patients must be kept warm and the temperature monitored. Blood loss must be measured and replaced early as these patients are often  $\beta$ -adrenergic blocked and tolerate blood loss poorly. When ganglionectomy is to be performed, inadvertent stimulation of the carotid sinus by the surgeon must be avoided. Precautions against air embolism should also be taken.

Induction of anesthesia can be achieved with several agents. Thiopental has so far been the most commonly used agent for induction in patients with LQTS (16,29,49,52). Thiamylal has also been used (50,51). Thiopental prolongs the QTI in normal patients (53), but its action on the QTI in patients with LQTS is unknown. However it has not been implicated in causing dysrhythmias in LQTS, and therefore is the agent of choice for induction of anesthesia. Ketamine should be avoided.

Tracheal intubation must be performed with the patient deeply anesthetized. To maximally decrease the sympathetic response to tracheal intubation, both topical and general anesthesia can be used (48), or a small dose of propranolol or lidocaine (51) can be given intravenously. Blind nasal intubation has also been recommended (48).

*Muscle relaxants.* Suxamethonium has been used for intubation without precipitation of dysrhythmias in spite of its effects on the autonomic system (16,29). Alcuronium (49), metocurine, and the newer non-depolarizing neuromuscular blockers are the agents of choice due to their limited release of histamine and their minimal effects on the autonomic nervous system (54). Pancuronium has produced ventricular fibrillation in a patient with LQTS (49), probably due to its sympathomimetic and parasympatholytic action, and therefore it and gallamine are contraindicated. At the conclusion of surgery, reversal of muscle relaxants with neostigmine and atropine, or glycopyrrolate, does not appear to adversely affect the QTI.

*Maintenance.* Anesthesia is maintained with oxygen, nitrous oxide, and an inhalational agent or nar-

cotic. Halothane (29,47), enflurane (24,29), and isoflurane have been used. Isoflurane is the preferred agent because it does not sensitize the myocardium to catecholamines (55), provides cardiovascular stability, and has a beneficial action on the QTI (48,51). Halothane, because it does sensitize the myocardium to catecholamines, is a poorer choice in LQTS. A deep level of anesthesia should be maintained throughout the procedure with supplemental analgesics given as necessary. Normal fluid and electrolyte must be maintained to prevent any abnormality that may prolong the QTI.

A Valsalva maneuver can prolong the QTI (especially in patients not on  $\beta$ -adrenergic blockers). Therefore a pattern of positive pressure ventilation with a long inspiratory phase, an end inspiratory plateau, high peak pressures, and a high inspiratory to expiratory ratio should be avoided in patients with LQTS (38).

### *Local or Regional Anesthesia*

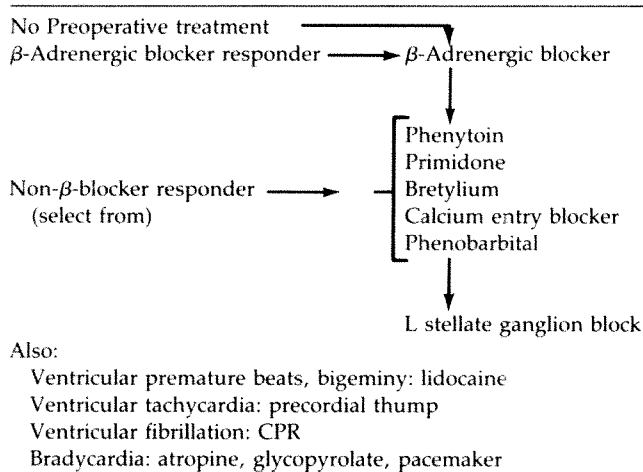
The principles involved in the management of a patient for a local or regional technique are the same as those for general anesthesia. Anxiety, an important cause of dysrhythmias in the LQTS, may not be readily controlled with the patient awake. There are very few reports of the specific use of regional techniques in these patients, but in a patient subsequently diagnosed as having LQTS, spinal anesthesia was uneventful on two occasions (24). Therefore it appears that local anesthesia can be used, but with caution. The solutions used should not contain epinephrine.

### *Prevention and Treatment of Dysrhythmias during Anesthesia*

Patients who respond to treatment with  $\beta$ -adrenergic blockers are unlikely to develop serious ventricular dysrhythmias during anesthesia, but should these occur they can be treated with an additional dose of  $\beta$ -adrenergic blocker. The management of those patients who have not responded to treatment with a  $\beta$ -adrenergic blocker alone is difficult. Phenytoin (24), primidone (44), bretylium (1), or verapamil (45) may be tried. Because of the complex drug interactions that a combination of antidysrhythmic agents may produce, a left stellate ganglion block should be considered if one or two drugs have been used without success (Table 2).

Lidocaine may be useful for ventricular premature beats and bigeminy in both groups (24,46). Ventricular tachycardia has responded best to early treatment by a precordial thump and external cardiac massage (46,48,49). Sinus bradycardia has been treated with

**Table 2.** Treatment and Prevention of Dysrhythmias in Patient with LQTS during Anesthesia



small doses of atropine (16), but there are patients with LQTS who do not respond to atropine (14), and a pacemaker may then be required.

### Emergence and After Surgery

Emergence from anesthesia and extubation are associated with an increased risk of developing dysrhythmias. Extubation should either be done during the stage of surgical anesthesia (48), or be preceded by another small dose of a  $\beta$ -adrenergic blocker or intravenous lidocaine. Monitoring must continue in the recovery area and stimuli must be kept to a minimum (24). For the first 24 hr after surgery it is advisable to admit the patient to an intensive care unit where continuous ECG monitoring is undertaken. Adequate analgesia must be provided and the patient should be disturbed as little as possible; even auditory stimuli have initiated ventricular fibrillation (56).  $\beta$ -adrenergic blockade must be continued by intravenous means in the immediate postoperative period with the dose of  $\beta$ -blocker gradually reduced or changed to the oral route according to the patient's response.

### Acquired Prolonged QT Interval Syndrome

Acquired prolongation of  $QT_c$  (ALQTS) is a separate syndrome. Its association with life-threatening dysrhythmias is, however, similar to LQTS. Ventricular dysrhythmias, especially torsade de pointes, occur with ALQTS.

### Causes of ALQTS

The causes of ALQTS are numerous (Table 3), and more are being recognized (5,16,17,27,31,50,53,57-65).

**Table 3.** Causes of an Acquired Prolonged QTI

Cardiac (5,57,58)	
Myocardial ischemia	
Acute carditis, e.g., rheumatic fever	
Acute cor pulmonale	
Cardiomyopathy	
Mitral valve prolapse	
Sinus bradycardia	
A-V block	
Thermal and electrolyte disturbances (5,57,58)	
Hypothermia	
Hypocalcemia	
Hypokalemia	
Hypomagnesemia	
Drugs (5,16,17,27,31,53,56-62)	
Antidysrhythmic agents	
Class Ia	Quinidine, procainamide, disopyramide
Ib	Lidocaine
II	$\beta$ blockers
III	Bretylium, amiodarone
IV	Pretilamine, lidoflazine (calcium entry blockers)
Digoxin overdose	
Anesthetic drugs	
Thiopental	
Succinylcholine	
Epinephrine	
Norepinephrine	
Psychotropic agents	
Phenothiazines	
Tricyclic compounds—imipramine	
Other	
Lithium	
Probutol	
Nervous system (5,50,58,63,64)	
Head injury	
Cerebrovascular accident (particularly intracranial hemorrhage)	
Neurosurgical procedures	
Sympathetic nervous system stimulation	
Radical neck surgery	
Transabdominal truncal vagotomy	
Endocrine and metabolic (31,57,58,63)	
Pheochromocytoma	
Adrenal insufficiency	
Ingestion of a liquid high protein diet	
Amyloidosis	
Hyperuricemia	
Kawasaki syndrome	
Hepatic dysfunction	

The causes are most readily divided into five main groups: cardiac disturbances, thermal and electrolyte disturbances, drugs, neurological, and endocrine or metabolic disturbances. The prolongation of the QTI is related to ventricular depolarization and repolarization. These are determined by the flux of sodium, potassium, and calcium. The energy for these ionic movements is supplied by the ATPase pump with magnesium as a cofactor. It is possible, therefore, that any abnormality altering sodium, potassium, magnesium, or calcium flux in cardiac muscle or con-

ducting tissue may alter the QTI, a scenario that accounts for the numerous causes of ALQTS.

### *Treatment of ALQTS*

It is important to make a clear distinction between LQTS and ALQTS.  $\beta$ -adrenergic blockers prolong the QTI in normal subjects and probably in patients with ALQTS as well, but they decrease the QTI in patients with LQTS (36). Isoproterenol, on the other hand, shortens the QTI in patients with ALQTS (36) and, though used in the treatment of ALQTS, is contraindicated in LQTS.

The first line of treatment of ALQTS must be the correction of any underlying cause, especially electrolyte disturbances (70). Drugs causing ALQTS should have their dosage reduced preoperatively according to the patient's requirements. This is best done in consultation with the attending physician or psychiatrist.

Dysrhythmias, when they occur, should initially be treated with the appropriate antidysrhythmic drug. However, when the dysrhythmia does not respond to conventional treatment and is recurrent (or the underlying cause is unknown or not readily reversible, but is due to a prolonged QT<sub>c</sub>), then a cautious infusion of isoproterenol can be tried (71). Another alternative is to use an electrical pacemaker, which has also been effective in controlling the rhythm disturbances in ALQTS (70).

### *Anesthesia and ALQTS*

Many of the causes of the ALQTS occur during the perioperative period. Some of these causes are reversible while others are not. In the preoperative period, patients with cardiac or CNS pathology, patients receiving antiarrhythmics or psychotropic drugs, or patients who have electrolyte disturbances, should be suspected for the presence of ALQTS. This is best excluded by assessing the QT<sub>c</sub> on the ECG.

Mitral valve prolapse may, rarely, be associated with a prolonged QT<sub>c</sub> (66). In these patients there is a high risk of dysrhythmias occurring during anesthesia, either due to the effect of hemodynamic changes on the prolapsing leaflet (67), or as a result of the prolonged QT<sub>c</sub>. Several anesthetics have been shown to alter the QT<sub>c</sub>. Thiopental, for example, prolongs the QT<sub>c</sub> within 90 sec after injection (53). Succinylcholine also prolongs the QT<sub>c</sub> in adults (53). The prolongation produced by succinylcholine is prevented by pretreatment with *d*-tubocurarine (53). It is interesting to note that the incidence of dysrhythmias was found to be significantly less in patients in whom the

increase in QT<sub>c</sub> was prevented by pretreatment with *d*-tubocurarine (53). The inhalation agents have not been assessed for their effects on the QT<sub>c</sub> in normal patients. Isoflurane appears to shorten the QT<sub>c</sub> in patients with LQTS (48,51). This does not, however, necessarily imply the same action in normal individuals. The effect of anesthetics on the QT<sub>c</sub> and the subsequent incidence of dysrhythmias warrants further investigation.

Electrolyte changes that may occur during anesthesia can also be important in altering the QT<sub>c</sub>. Massive blood transfusion may result in the citrate of donor blood binding magnesium (68) and calcium. Hypomagnesemia and hypocalcemia are known to prolong the QT<sub>c</sub> (57). Hypomagnesemia can also occur in patients treated with diuretics and in chronic alcoholics (69). Hypokalemia, another important cause of ALQTS (57), can be found during anesthesia due to fluid shifts or alterations in acid-base balance. Hypothermia, which may occur spontaneously or be induced intraoperatively, also produces a prolonged QT<sub>c</sub> (5). Certain operations may also be associated with prolongation of the QTI, especially those about the head and neck (63,64), and transabdominal truncal vagotomy (58).

Often a combination of factors that are known to prolong the QT<sub>c</sub> result in clinically evident ALQTS and the associated dysrhythmias (70,71). Thus patients with ALQTS may present either preoperatively or intraoperatively. It is therefore necessary to be aware of those patients presenting preoperatively and to have a high index of suspicion when dysrhythmias occur intraoperatively.

### *Summary*

The prolonged QT interval syndromes consist of two forms, one congenital and one acquired. The congenital form is probably due to an imbalance in the sympathetic nervous system supply to the heart. It is a preventable cause of sudden death both at an early age and during anesthesia. Recognition of congenital forms of prolonged QT interval and treatment with  $\beta$ -adrenergic blockers have reduced the mortality. Special care in the perioperative period is necessary to prevent anesthetic-related deaths. The acquired form has many causes. These may be present preoperatively or they may occur intraoperatively. It is important that patients with ALQTS are recognized early and the underlying cause treated.

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## Review Article

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# Croup and Epiglottitis in Children: The Anesthesiologist as Diagnostician

James H. Diaz, MD, FAAP

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The techniques for early diagnosis and management of airway obstruction in children with croup (laryngotracheobronchitis) and epiglottitis remain controversial. Epiglottitis or, more appropriately, supraglottitis, is an acute fulminant bacterial inflammation of supraglottic structures including epiglottis, arytenoids, aryepiglottic folds, and uvula (1,2) (Fig. 1). Croup, on the other hand, is a more insidious viral syndrome causing progressive inflammation and edema of the entire subglottic tracheobronchial tree (3-5) (Fig. 1). Epiglottitis quickly produces rapid inspiratory airway obstruction, while croup results in gradually worsening inspiratory stridor progressing to fatigue and respiratory failure. Early differentiation of croup and epiglottitis avoids the catastrophic consequences of sudden complete supraglottic airway obstruction associated with acute epiglottitis, and permits proper management of subglottic airway obstruction in croup to reduce the likelihood of developing subglottic granulomas, tracheomalacia, and subglottic stenosis.

This review compares the etiology, epidemiology, pathology, and clinical findings of croup and epiglottitis, which should aid physicians in developing a practical approach to rapid differential diagnosis and early appropriate therapeutic intervention based on anatomic and physiologic principles.

## Etiology

Sinclair (6), and later Jones and Camps (7), were among the first to demonstrate that acute epiglottitis in children is usually caused by *Haemophilus influenzae* type b. Since then, others have demonstrated that epiglottitis can, in rare cases, be caused by other bacterial

agents such as *Staphylococcus aureus* (8),  $\beta$ -hemolytic streptococci (8,9), and *Diplococcus pneumoniae* (10). Nonbacterial croup, as initially described by Rabe (11), was characterized by the absence of any consistent bacterial pathogen; and was later demonstrated by Chanock (12) to be the result of parainfluenzae myxoviruses (>30%), respiratory syncytial virus (6%), adenovirus type 5 (4%), or, in rare cases, echoviruses and influenzae viruses.

## Epidemiology

Characteristic incidences, antecedent illnesses, age and sex differences, geographic and climatic differences, and even seasonal variations have been described for croup and epiglottitis. Croup is the most common infectious form of acute and subacute upper airway obstruction in infants and children; epiglottitis and laryngeal diphtheria are much less common (13).

Croup usually occurs in the infant or child younger than three years and is heralded by nighttime respiratory stridor, hoarseness, and barking, high-pitched cough (5). Acute epiglottitis occurs most often in older children, two to seven years old, and occasionally in adults. Males have a slightly higher risk of developing acute epiglottitis (8,14,15).

Croup and epiglottitis are both diseases of drier, temperate zones, and most cases appear to cluster during the colder winter months, particularly during the months of greatest seasonal change, such as October, November, March, and April (14,16). Large industrial northeastern cities [Pittsburgh (17), Newark (18), Buffalo (19), Montreal (20)] and large midwestern and western communities [Cincinnati (21), Salt Lake City (22), Denver (23)] consistently report the greatest number of cases of croup and epiglottitis, suggesting possible epidemiologic roles for endemic causative agents, air pollution, and lack of humidity.

Infectious transmission of agents causing croup and epiglottitis has not been well studied. Airborne transmission and inhalation of viruses is likely in croup. Person-to-person spread of *H. influenzae* type b has

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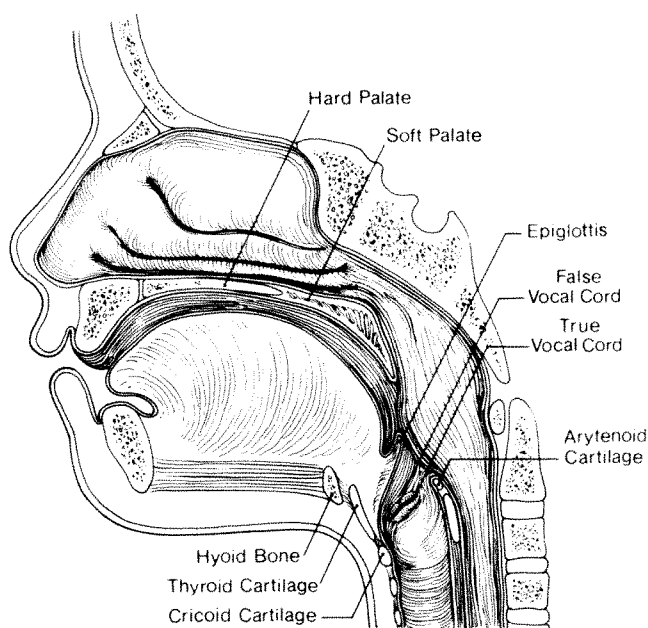


Figure 1. Midsagittal section of the normal childhood larynx. The glottic aperture between the true vocal cords delineates the extrapulmonary airway into the upper or supraglottic airway and lower or subglottic airway. (Reprinted by permission from Diaz JH. Controversies in the diagnosis and management of common upper airway infections. ER Reports 1983;4:25.)

been documented in epiglottitis (24). Ginsburg (24) recently described the almost simultaneous occurrence of *H. influenzae* meningitis, septic arthritis, and epiglottitis in three siblings. Finally, host factors such as prior infections or immunosuppression may also influence susceptibility to both croup and epiglottitis (9,25).

## Pathology

Croup produces progressive inflammatory edema in the subglottic larynx, trachea, mainstem, and segmental bronchi (Fig. 1). Progressive narrowing of extrathoracic, lower airway diameter at the cricoid level produces the inspiratory stridor of croup (Fig. 1).

Epiglottitis produces massive inflammatory edema, which may lead to ulceration and submucosal abscess formation with necrosis at and above the level of the true vocal cords. The mucosa of the epiglottis, arytenoids, false vocal cords, posterior tongue, and even uvula may become violaceous in color and massively swollen, precipitating acute, complete supraglottic airway obstruction (2). Shackelford (26) has recently described radiographic subglottic edema in acute epiglottitis. This subglottic narrowing may be congenital or acquired. Congenital subglottic stenosis may predispose children to recurrent croup, or it may coexist with acute epiglottitis (26).

## Pathophysiology

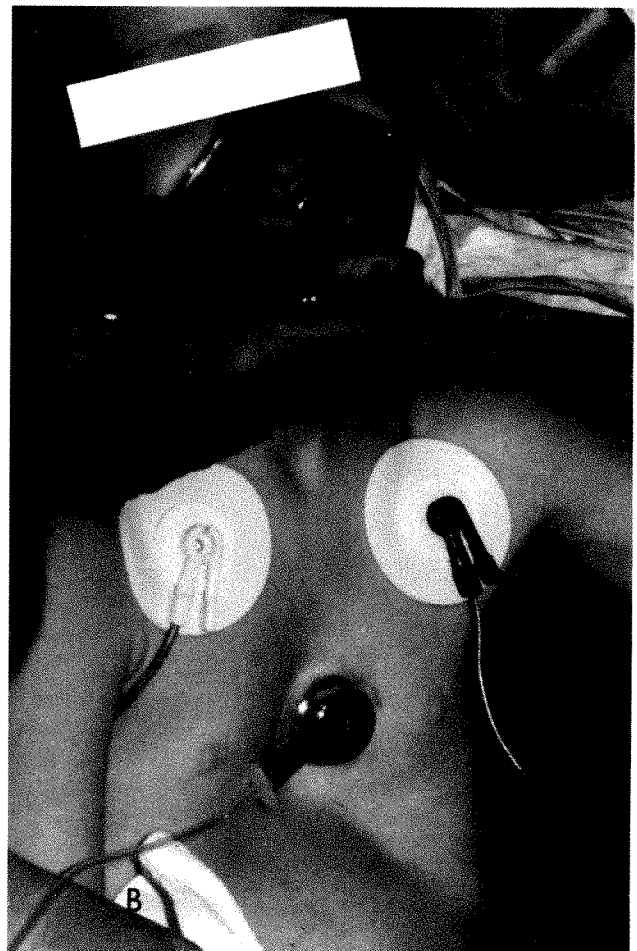
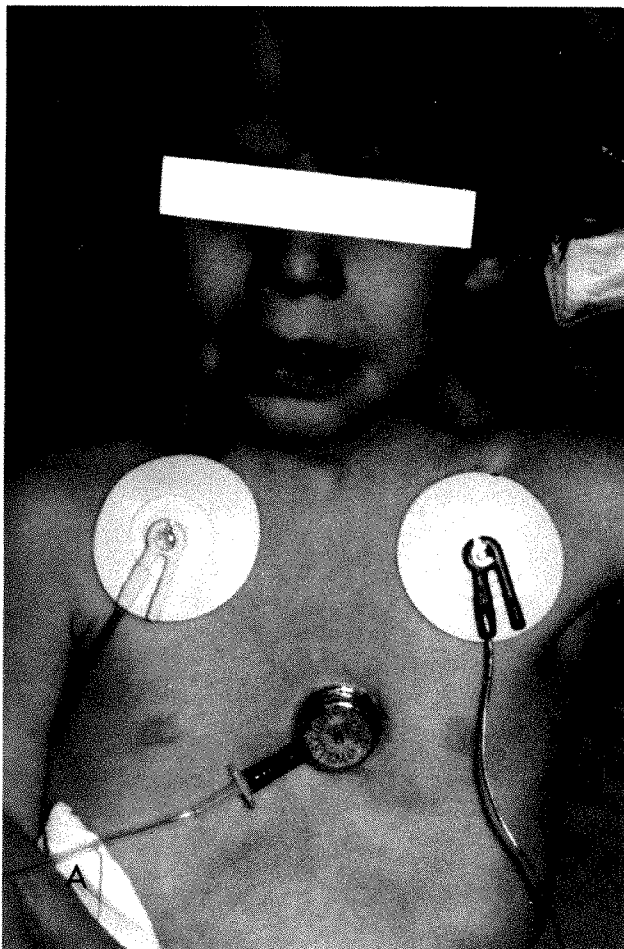
In croup, the greatest resistance to airflow occurs at the narrowest part of the extrathoracic airway—the cricoid ring in preadolescent children (Figs. 1,2). The progressive edematous narrowing at the cricoid level of the larynx produces the inspiratory stridor of croup. The more diffuse tracheobronchitis of croup causes tachypnea and cough. Resistance to air flow at the narrowed subglottic area produces turbulence, and gives a high-pitched sound to the croupy cough. The tachypnea and increased work of breathing may eventually lead to fatigue with hypercarbia, hypoxemia, and respiratory failure.

In epiglottitis, the rapidly evolving course of fever, sore throat, dysphagia, dysphonia, and inspiratory airway obstruction results from bacterial inflammation of the epiglottis and contiguous supraglottic structures. Reduced airflow produces only muffled stridor at the vocal cords and little coughing. Dysphonia, and later aphonia, characterize acute epiglottitis and are manifestations of diminished to no air flow. Successful manual ventilation by reservoir bag and face mask during cardiopulmonary resuscitation or inhalation anesthesia in children with epiglottitis suggests that the epiglottis does not plug the glottis to totally obstruct the airway (22,27–29). Jones has suggested that as the epiglottis and aryepiglottic folds become edematous, they also become rigid, preventing any obstructing movement of the epiglottis (30). In any event, anesthesiologists should remember this and quickly employ bag and mask ventilation should severe airway obstruction occur (22,27–29).

Stridor during croup and epiglottitis is produced by the flow of air during ventilation through an obstructed extrathoracic airway. Stridor may be loud, high-pitched, and often musical in croup, but soft and harsh in epiglottitis, depending on the type and extent of obstruction and ensuing flow dynamics (31). The inspiratory stridor of croup and epiglottitis indicates extrathoracic airway obstruction, while expiratory and biphasic respiratory stridor generally point to intrathoracic airway obstruction commonly noted with a bronchial foreign body (31).

Finally, a characteristic airway-preserving posture is usually assumed by children with acute epiglottitis. This protective posture is a sitting position with forward flexion at the waist, slight cervical flexion, forward chin thrust, and tripod placement of the supporting upper extremities (Fig. 2(A)). This characteristic sitting posture is almost pathognomonic of acute epiglottitis, and aids in rapid differentiation from croup. It also allows head position, gravity, and mandibulo-facial musculature to tilt the swollen epiglottis off the





glottic aperture (Fig. 2(A)). Any deviation from this characteristic posture may, in fact, worsen airway obstruction (Fig. 2(B)).

### Historical Findings

Usually croup has a gradual onset during an upper respiratory illness in an infant or child three years old or younger (Table 1). The voice weakens, and hoarseness with a barking cough develops. Inspiratory stridor may develop within another 6–24 hr that, if severe, will be associated with suprasternal and supraclavicular retractions. Constitutional symptoms of malaise, anorexia, and low-grade fever with lethargy will persist. In room air, cyanosis may develop in severe cases.

Epiglottitis develops rapidly in an older child or, more rarely, in an adult without a preceding coryza, and is characterized by abrupt onset of high fever (38–41°C), irritability, lethargy, and very sore throat. These symptoms will shortly lead to the pathogno-

**Figure 2.** A characteristic sitting posture with slight cervical flexion, forward chin thrust, and mild flexion at the waist is almost pathognomonic of epiglottitis and aids in rapid differentiation from croup. (A) Suprasternal and supraclavicular retractions indicative of moderate upper airway obstruction are apparent. Any deviation from this protective posture exacerbated airway obstruction. (B) Even the minimal cervical extension necessary for proper lateral neck roentgenography as simulated caused nearly complete inspiratory airway obstruction with marked substernal and subcostal retractions.

monic signs of dysphagia, dysphonia, drooling, and inspiratory respiratory distress (the four "D's"). As noted, the seasonal variation for both croup and epiglottitis is the same.

### Physical Examination

The infant or child with croup initially appears to have a mild systemic illness with lethargy and low-grade fever (Tables 2,3, Fig. 2). Hoarseness and barking cough will be present with either normal or harsh breathing sounds. Croup may often be diagnosed over the tele-

phone as the child's crowing inspirations and barking cough provide obvious background accompaniment to the mother's anxious questions (4). Inspiratory wheezing and rhonchi may develop later. As the course of the illness progresses, weakening inspiratory stridor and diminished breathing sounds reflect decreasing airflow. Cyanosis, in room air, and marked inspiratory retractions will develop in severe cases. Coughing becomes less as the child fatigues. Tachypnea, labored ventilation, and cyanosis in O<sub>2</sub> mark the onset of respiratory failure, which, if improperly managed, may result in cardiopulmonary arrest with hypoxic brain damage or death. Recently, Downes (32) proposed a practical scoring system for upper airway obstruction in croup based on physical findings that may prove very helpful in assessing the course of the illness and selecting appropriate early therapeutic interventions (Table 2).

The clinical course of epiglottitis is acute and fulminating. The child appears to have a serious toxic illness with high fever and sore throat that progresses from dysphagia, drooling, and dysphonia to severe airflow obstruction with diminishing breathing sounds and little stridor or cough. The airway-protective sitting posture with chin thrust forward is characteristic of epiglottitis, and should be maintained as high inspired O<sub>2</sub> concentrations are provided and preparations are made for artificial airway insertion. Cyanosis in spite of high inspired O<sub>2</sub> concentrations is common, as the toxic nature of the disease combines with progressively labored ventilation to increase tissue O<sub>2</sub> demand when alveolar O<sub>2</sub> supply is limited by upper airway obstruction. As airflow diminishes, inspiratory retractions become more apparent in suprasternal, substernal, supraclavicular, intercostal, and subcostal regions (Fig. 2(A),(B)). Fatigue develops rapidly from labored ventilation. Cardiopulmonary arrest will occur quickly if oxygenation and ventilation are not provided early in the course.

## Radiographic Evaluation

Lateral neck and chest roentgenograms may be quite useful in evaluating pediatric upper airway obstruction, in identifying associated pulmonary complications, and in confirming proper positioning of artificial airways and nasogastric tubes (Table 4, Figs. 3,4). Radiologic evaluation does not, however, always correlate with clinical severity or provide exact diagnoses, and may worsen airway obstruction by interfering with protective postures (Fig. 2(B)) (33). Radiologic examination appears most beneficial in locating foreign bodies, identifying subglottic edema or stenosis, following pulmonary infiltrates, and direct-

Table 1. Historical Findings: Croup and Epiglottitis

Historical findings	Croup	Epiglottitis
Onset	Gradual	Abrupt
Constitutional symptoms	Mild	Severe
Cough	Barking	Weak to none
Sore throat	Present	Severe
Dysphagia	May be present	Severe
Voice changes	Hoarseness	Muffled dysphonia progressing to aphonia
Drooling	Absent	May be present

ing chest physiotherapy. Cervical x-rays will help to differentiate such nonacute causes of inspiratory stridor as croup, foreign body aspiration, retropharyngeal abscess, and congenital anomalies.

Many authorities recommend immediate lateral neck films for noninvasive differentiation of croup and epiglottitis, insisting that any oropharyngeal examination might provoke complete airway obstruction in cases of epiglottitis (34,35). Others warn of the dangers of time-consuming procedures in the x-ray suite, cervical hyperextension, and interference with protective postures, preferring early direct pharyngoscopy for epiglottic visualization (Fig. 2(B)) (36). A few authors disdain both early radiologic or endoscopic evaluation of acute airway obstruction, preferring initial treatment with intravenous steroids and antibiotics before intervening (27,29,37). Such measures may prove successful in certain forms of upper airway obstruction in adults, but carry a high risk in children because of small airway caliber, and are not recommended (18,38).

If time and clinical severity of airway compromise permit, radiologic examination of the child with upper airway obstruction will usually be abnormal and often diagnostic. Many radiographic features of acute upper airway obstruction, however, are shared by both croup and epiglottitis (Table 4). Shared features include hypopharyngeal dilatation and inspiratory tracheal collapse (33) (Table 4). The characteristic radiologic features of epiglottitis include thickening of epiglottic tissues and almost complete obliteration of the valleculae and pyriform sinuses (39,40) (Fig. 3(A)). A rounded thickening of the epiglottic shadow on lateral neck projection, giving both the configuration and approximate size of an adult thumb ("thumb" sign), has been aptly described by Podgore and Bass (41) (Fig. 4(A)). Podgore and Bass (41) have also stated that lateral neck films of children with upper airway distress without epiglottic involvement contain a nor-

Table 2. Downes Scoring System for Upper Airway Obstruction (32)

Physical finding	Score		
	0	1	2
Stridor	None	Inspiratory	Inspiratory and expiratory
Cough	None	Hoarse cry	Bark
Retractions and nasal flaring	None	Flaring and suprasternal retractions	Flaring and suprasternal, subcostal, intercostal retractions
Cyanosis	None	In air	In 40% O <sub>2</sub>
Inspiratory breath sounds	Normal	Harsh, with wheezing or rhonchi	Delayed

Maximum score is 10. Normal score is 0. Score of 4 or more requires therapy. Patient with score of 7 or more not responding to medical management may require immediate insertion of an artificial tracheal airway (32).

Table 3. Physical Findings: Croup and Epiglottitis

Physical findings	Croup	Epiglottitis
Protective posture	Absent	Present
Fever	Low	High
Cyanosis	Usually absent	Usually present
Stridor	Present	Mild to none
Nasal flaring	May develop	Usually present
Retractions	Initially mild when occur	Initially marked
Diaphragmatic and abdominal excursions	Not usually apparent	Marked
Heart rate	Sinus tachycardia	Sinus tachycardia, bradycardia with severe hypoxia and preceding cardiac arrest
Respiratory rate	Tachypnea	Tachypnea

mal epiglottic shadow having the configuration of an adult's little finger ("little finger" sign) (Fig. 4(B)). The "little finger" sign does not, however, unequivocally rule out acute epiglottitis, as Diaz and Lockhart have demonstrated in a review of 104 cases with 14 out of 20 false positive x-rays (15) (Fig. 4(B)).

The characteristic radiographic features of croup include blurring of the tracheal air shadow on lateral neck projection and symmetrical narrowing of the subglottic air shadow ("church steeple" sign) on anteroposterior projection (33) (Fig. 4).

Recently, Shakelford (26) identified localized subglottic edema in children with epiglottitis, radiographically indistinguishable from that seen in croup. The clinical significance of this new finding is threefold: a) acute epiglottitis may not always be a completely supraglottic inflammation; b) congenital subglottic stenosis may occur in combination with croup and epiglottitis; and c) even characteristic x-ray features may be shared by several types of upper airway obstruction.

In conclusion, radiologic evaluation may be quite helpful in croup and other insidious forms of upper airway obstruction, but cannot be recommended as the initial diagnostic procedure in suspected epiglot-

titis. Lateral neck films may prove time-consuming, nondiagnostic, or even harmful in some children with acute epiglottitis (33,36).

## Laboratory Evaluation

### White Blood Cell Count

Leukocytosis occurs in both croup and epiglottitis. Total white blood cell count approaches 15,000–25,000 in epiglottitis, with polymorphonuclear leukocytes and immature forms predominating (>75%) (5). Total white blood cell count usually remains below 12,000 in croup, with a relative lymphocytosis (>30%) characteristic of viral diseases.

### Arterial Gas Tensions

Hypoxemia occurs in room air in both diseases, and may not respond to high inspired O<sub>2</sub> concentration in epiglottitis. Normal or elevated PaCO<sub>2</sub> suggests fatigue in either croup or epiglottitis (5).

### Microbiology

Accurate bacteriologic diagnosis and antibiotic sensitivity testing in epiglottitis are now becoming more

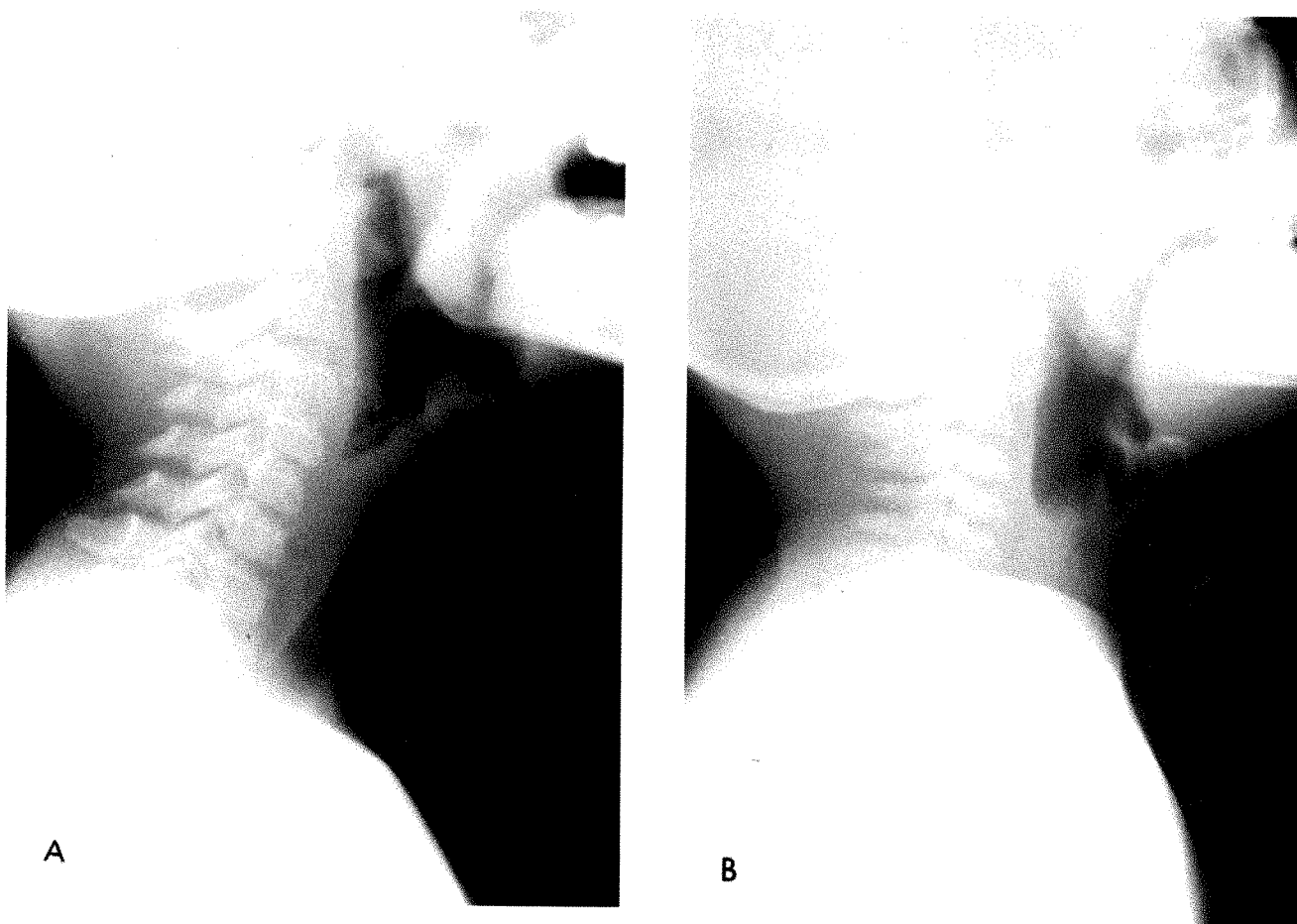


Figure 3. Lateral neck roentgenograms in patients with acute epiglottitis. (A) a grossly swollen, thumb-sized epiglottis, (B) a normal, little-finger-sized epiglottis with hypopharyngeal dilatation as only indication of upper airway obstruction. (Reprinted by permission from Diaz JH, Lockhart CH. Early diagnosis and airway management of acute epiglottitis in children. *South Med J* 1982;75:399.)

important as ampicillin-resistant strains of *H. influenzae* type b become more commonplace (>10% in some series) (42). Recently, even chloramphenicol-resistant strains of *H. influenzae* type b have been isolated (43). The transient bacteremia of nasotracheal intubation has been used to significantly increase the yield of positive blood cultures for early antibiotic susceptibility testing in epiglottitis, without increasing the risk of metastatic foci of infection (15,44). Systemic bacteremia with *H. influenzae* can usually be identified in 50% or more cases of epiglottitis (14,15). Blood cultures are always more reliable than pharyngeal-epiglottic cultures in isolating causative organisms (42). Septic arthritis, meningitis, pericarditis, and otitis media may, in rare cases, accompany epiglottitis, and necessitate diagnostic paracenteses or spinal taps with counterimmunoelectrophoresis stud-

Figure 4. A characteristic radiographic feature of croup is symmetrical narrowing of the subglottic air shadow, "church steeple" sign, as demonstrated on anteroposterior neck film. (Reprinted by permission from Diaz JH. Controversies in the diagnosis and management of common upper airway infections. *ER Reports* 1983;4:25.)

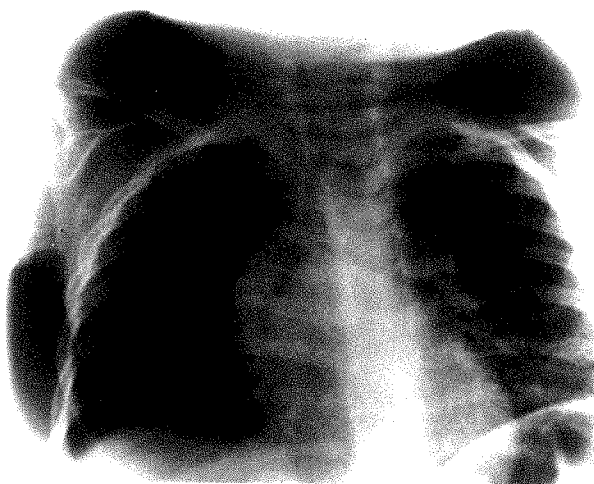




Table 4. Radiographic Evaluation: Croup and Epiglottitis (Figs. 3, 4)

Radiographic features	Croup	Epiglottitis
Shared features		
Hypopharyngeal dilatation (lat)	Present	Present
Inspiratory tracheal collapse (lat)	Present	May be present
Subglottic edema (lat)	Present	May be present
Characteristic features <sup>a</sup>		
"Church steeple" sign (AP)	Present	Absent
"Thumb" sign (lat)	Absent	Present
"Little finger" sign (lat)	Present	Usually absent
Associated features (CXR)		
Pulmonary infiltrates	May be present	May be present
Pulmonary edema	May be present	May be present

<sup>a</sup>Not entirely characteristic features but certainly reliable when present and correlated with clinical findings.  
Abbreviations: lat, lateral neck projection; AP, anteroposterior neck projection; CXR, chest x-ray.

ies to detect capsular antigens of *H. influenzae* when cultures are negative (14,45). Viral cultures do not appear to offer any clinical benefits in patients with croup, but do provide significant epidemiologic information during seasonal outbreaks. Sputum cultures and diagnostic thoracentesis may be necessary for evaluation of pneumonia or empyema complicating croup or epiglottitis. Immunocompromised children appear at greater risk of developing sepsis and serious secondary infections during the course of croup or epiglottitis (9,25).

### Rapid Differential Diagnosis

Such anatomic factors as a small mouth and nares; large tongue; anterocephalad glottic orifice; large, drooping, U-shaped epiglottis; and narrow cricoid ring predispose the child to early airway obstruction during upper respiratory illnesses. Several disorders (Table 5) may produce acute upper airway obstruction in children.

The rapid, early diagnosis of croup and epiglottitis in children depends on accurate assessment of historical and physical findings; and on such confirmatory investigations as lateral neck roentgenograms and, most importantly, direct pharyngoscopy. Direct pharyngoscopy has proven to be quicker, safer, and more reliable than lateral neck films in diagnosing epiglottitis (36). It can be performed without disturbing the patient's protective posture (by using the curved blade as a tongue depressor), provides for immediate airway establishment by endotracheal intubation, and quickly differentiates epiglottitis from croup without precipitating laryngospasm or bleeding if appropriate technique is used. Direct pharyngoscopy should be performed by experienced anesthesiologists on suspicion of epiglottitis either in an emergency room, operating room, or anesthesia induction area where

Table 5. Causes of Acute Extrathoracic Airway Obstruction in Children

Infectious	Congenital <sup>a</sup>	Traumatic or acquired
Croup	Subglottic stenosis	Foreign body aspiration
Epiglottitis	Laryngeal webs	Laryngeal fracture
Diphtheria	Vascular rings	Inhalation burns
	Laryngomalacia	Vocal cord paralysis
		Subglottic edema
		Post intubation
		Anaphylaxis

<sup>a</sup>Acute upper airway obstruction usually in the presence of edema or infection.

capabilities for tracheal intubation, tracheostomy, general anesthesia, and mechanical ventilation are at hand. After 5 min of mask preoxygenation with 100% O<sub>2</sub>, a curved pediatric laryngoscope blade (Macintosh No. 2) is introduced on the right side of the mouth, gently depressing the anterior two-thirds of the tongue in the midline to expose the epiglottis, with care taken not to touch the epiglottis or expose the glottis. Identifying a cherry-red, edematous epiglottis is an indication for immediate airway establishment by endotracheal intubation. Visualizing a normal-sized epiglottis suggests other causes of inspiratory airway obstruction such as croup, foreign body aspiration, or congenital anomaly. If clinical conditions permit, humidified O<sub>2</sub> can be provided, and further historical and diagnostic investigations undertaken.

Noninvasive diagnostic techniques, such as observation for worsening airway obstruction, carry a high mortality in epiglottitis and are not recommended (5). Temporizing measures, such as racemic epinephrine by vaporization or positive pressure inhalation, may improve croup but not epiglottitis (32,46). Direct pharyngoscopy under ideal conditions by experienced personnel is a proven and safe method of early definitive diagnosis of severe croup and epiglottitis (19,36).

Table 6. Management: Croup and Epiglottitis

Principles of management	Croup	Epiglottitis
Oxygen	Essential	Essential
Airway	No intervention if possible, tracheostomy or short duration nasotracheal intubation	Nasotracheal tube or tracheostomy
Humidification	Essential	Essential
Aerosolized vasoconstrictors	Beneficial	Ineffective
Steroids	Unproven value	Unproven value
Antibiotics	Ineffective	Essential

### Initial Management of Acute Upper Airway Obstruction of Undetermined Etiology

While taking the history from parents, and during physical examination of the airway-compromised child, high inspired concentrations of O<sub>2</sub> must be provided to prevent hypoxemia and cardiac arrest. In cases of known or suspected foreign body aspiration, there is usually time for radiographic studies, inhalation anesthesia, and therapeutic bronchoscopy. If history and physical examination favor a diagnosis of croup, aerosol administration of a diluted racemic epinephrine solution may dramatically reduce subglottic edema, and obviate the need for an artificial airway (32,46). Once direct pharyngoscopy establishes a diagnosis of epiglottitis, an artificial airway, preferably a nasotracheal tube, is indicated.

In cases of acute airway obstruction with undetermined etiology, preoxygenation should be followed by direct diagnostic pharyngoscopy. Equipment for use by skilled individuals to intubate the trachea, perform tracheostomy, and ventilate the patient must be immediately available. Jaw thrust with head tilt and mouth-to-mouth or bag-valve-mask ventilation must be instituted until a controlled situation with appropriate equipment and help is established (47). Multiple attempts at tracheal intubation without preoxygenation by inexperienced personnel may prove lethal, particularly in cases of epiglottitis, laryngeal foreign body, or laryngeal fracture. Emergency tracheostomy without preoxygenation or prior tracheal intubation can also be disastrous (32). Cricothyrotomy may provide the only secure airway in certain situations (47).

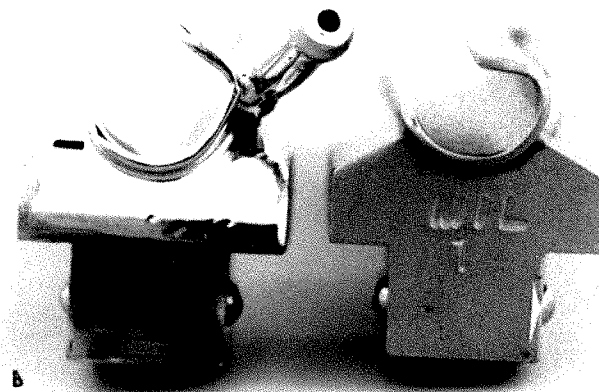
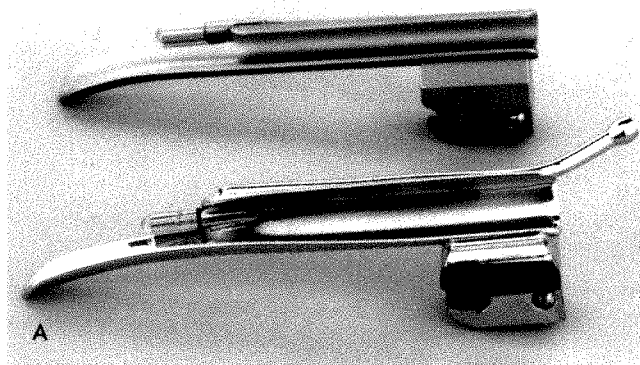
### Management of Epiglottitis

Selection of the best artificial airway in epiglottitis depends on the skills of the attending physicians and the availability of experienced pediatric intensive care nurses (Table 6). If complete airway obstruction or cardiac arrest occurs in the home, the physician's office, an ambulance, or aircraft, jaw thrust with head tilt in combination with mouth-to-mouth or bag-valve-

mask ventilation and external cardiac compression can be instituted without causing the epiglottitis to plug the glottis (27-29,47). Artificial translaryngeal or transtracheal airway placement by experienced personnel should follow. If personnel are unavailable, CPR can be continued (47).

### Airway Management of Epiglottitis

Many groups continue to recommend tracheostomy in anesthetized patients as the airway of choice in epiglottitis, insisting on endotracheal intubation of conscious or anesthetized patients by bronchoscope or oral endotracheal tube before operation (48,49). If the airway has been secured before elective tracheostomy, many believe that subjecting the child to a second procedure, with a significant risk of its own, is unnecessary (23,50). Nasotracheal or orotracheal intubation of conscious or anesthetized patients will provide a secure short-term artificial airway with little morbidity. Supine nasotracheal intubation of conscious patients with epiglottitis can often be accomplished after topical application of 4% cocaine to the nasal mucosa and 5 min of mask preoxygenation with 100% O<sub>2</sub> with the child in the seated position (Fig. 2). Utilizing the techniques recommended for direct pharyngoscopy, direct laryngoscopy can be performed by introducing a curved blade on the right side of the mouth, depressing the tongue, and displacing it to the left of the oropharynx, with care taken to avoid contacting the inflamed epiglottis. Selection of the right, rather than the left, nostril may permit more intraoral working room for Magill forceps with better direct visualization when using curved laryngoscope blades. Direct laryngoscopy for tracheal intubation, rather than blind nasotracheal intubation, is also recommended to avoid traumatizing the friable epiglottis. Often, the glottic aperture cannot be easily visualized with a curved blade. In these cases, careful midline observation for turbulent airflow causing tissue flapping or bubbling of oral secretions may pinpoint a glottis whose opening is occluded by edematous arytenoid cartilages and a distorted epiglottis.



In difficult cases, epiglottic contact and suspension by straight bronchoscope or Miller blade may be indicated, but carries the risk of hemorrhage, epiglottic fragmentation, and laryngospasm. Flexible fiberoptic broncholangoscopes permit easy glottic cannulation by experienced endoscopists under difficult conditions, but still require the subsequent blind telescoping of larger tracheal tubes past a friable epiglottis and into the trachea. In our experience, a modified O<sub>2</sub>-insufflating Miller blade has proven very useful in facilitating difficult tracheal intubation in acute epiglottitis (Fig. 5) (51).

Nasotracheal intubation with the child awake may be impossible in about 10% of patients with acute epiglottitis (15). These children are often older and larger, and may become uncooperative and restless from air hunger. They may come for treatment early in the course of their illness, before becoming fatigued by hours of labored ventilation. Inhalation anesthesia may be required for performing successful tracheal intubation in these patients. Knowledgeable anesthesia assistants and surgeons skilled in pediatric tracheostomy must be present during induction of anesthesia and endotracheal intubation in these cases. A variety of endotracheal tubes and laryngoscopes, Magill forceps, suction apparatus, and surgical instruments for tracheostomy should be at hand.

Mask induction with carefully titrated inspired halothane in 100% O<sub>2</sub> is recommended during spontaneous assisted ventilation with cricoid pressure. In the event of contraindication to halothane, isoflurane in 100% O<sub>2</sub> may be used, but experience is limited and it may carry more risk of coughing and laryngospasm due to odor and pungency. Adequate preoxygenation and a reliable intravenous line should be provided before induction. Premedication with intravenous atropine (0.01 mg/kg) may reduce the volume of oral secretions and prevent bradycardia from air-

Figure 5. A modified Miller-1 blade in the foreground with an opened C-flange, side-arm insufflation port and channel, and corrugated lingual surface. A standard Miller-1 blade is in the background for comparison. (B) Rear views of modified Miller-1 blade (left) and standard Miller-1 blade (right) demonstrating improved sighting capability and unobtrusive gas insufflation port on modified blade. (Reprinted by permission from Diaz JH. Further modifications of the Miller blade for difficult pediatric laryngoscopy. *Anesthesiology* 1984;60:612.)

way manipulations or vagotonic anesthetic agents. Muscle relaxants appear contraindicated in anesthetizing patients with epiglottitis because neuromuscular paralysis would not insure successful tracheal intubation, would remove any spontaneous ventilation, and could abolish the best and most manageable airway the patient has. Narcotic or barbiturate inductions would also appear contraindicated because of the potential for further cardiorespiratory depression in patients with epiglottitis. In the event of laryngospasm on induction or tracheal intubation, only tracheostomy or spontaneous resolution of laryngospasm would restore airflow. Once again, positive pressure ventilation by mask has been demonstrated to provide effective ventilation in cases of epiglottitis where tracheal intubation is delayed or impossible, or during preparations for tracheostomy (27-29,47).

Many experienced groups have now confirmed the safety of airway management by short term (12-48 hr) nasotracheal intubation in acute epiglottitis (16,20,23,52-55). Duration of tracheal intubation is shorter than with tracheostomy, and the length of hospital stay and cost of hospitalization are less (53,54). Tracheal air leaks (at 20-25 cm H<sub>2</sub>O external airway pressure) (56), small endotracheal tubes (internal diameter 0.5 mm smaller than age-predicted) (57), and short intubation times are important in reducing traumatic tracheal edema with granulation or later scarring.

Timing of tracheal extubation in epiglottitis is con-

troversial and must depend on clinical findings, and on direct visualization of the epiglottis at pharyngoscopy. Only when the edematous distortion and erythema have subsided sufficiently to permit unobstructed ventilation should the endotracheal tube be removed. The use of corticosteroids prior to tracheal extubation to reduce traumatic tracheal edema is debatable, and requires further clinical study. Conscientious securing of endotracheal tubes, appropriate arm restraints, and, occasionally, parenteral sedation (diazepam, 0.1–0.15 mg/kg, intravenously as needed) will greatly reduce the risk of accidental extubation, a common complication of therapy. Early chest physiotherapy and frequent sterile suctioning are essential in preventing obstructive mucus plugs and clearing of pulmonary infiltrates.

### Antibiotic Management of Epiglottitis

Early intravenous ampicillin therapy ( $50\text{--}200\text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ ) must begin on clinical confirmation of the diagnosis at pharyngoscopy (Table 6). Chloramphenicol ( $50\text{--}100\text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ ) may be added to ampicillin therapy initially, or may replace it when ampicillin-resistant strains are identified. Recent clinical trials have suggested that high-dose ampicillin therapy alone ( $200\text{--}400\text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ ) may be successful in the management of ampicillin-resistant *H. influenzae* infections (58). Chloramphenicol therapy is recommended in children with penicillin allergy. Chloramphenicol-resistant strains of *H. influenzae* may be eradicated with aminoglycosides (gentamicin and tobramycin), cotrimoxazole, or trimethoprim-sulfamethoxazole (42). Aminoglycosides have limited CNS penetrance, however, and would be of little value in rare combined cases of epiglottitis and meningitis (42). Parenteral antibiotic therapy should continue for at least 24 hr after extubation and may be followed by oral therapy for a period of 7–10 days.

An increased risk of invasive disease with bacteremia (e.g., meningitis, epiglottitis, septic arthritis, cellulitis) among household and day-care center exposed contacts has been demonstrated (24,43). The effectiveness of prophylactic antibiotic therapy for persons exposed to cases of epiglottitis is now under investigation (43). Currently, the Committee on Infectious Diseases of the American Academy of Pediatrics advises the following (43): 1) rifampin prophylaxis for all household contacts (children and adults) in households where there are children (other than the index case) younger than 4 years old; 2) nursery school and day-care center contacts (children and adults) should be considered "household" contacts; 3) rifampin prophylaxis is not recommended for pregnant contacts;

4) rifampin should be given orally once daily for 4 days in a 20 mg/kg dose (maximum dose, 600 mg/day); and 5) prior to hospital discharge, children recovering from epiglottitis should receive oral rifampin therapy to eradicate a common nasopharyngeal carrier state, and avoid the reintroduction of *H. influenzae* into households.

### Management of Croup

The cornerstones of medical management in croup are well accepted and include oxygen administration, intravenous hydration, and humidification of the tracheobronchial tree by mist vaporization or nebulization (Table 6). Antibiotics are of no benefit in a viral illness unless a secondary bacterial infection, usually pneumonia, intervenes. The role of corticosteroids in treating croup remains controversial, but they may be useful in occasional cases that become refractory to nebulized epinephrine solutions (59,60). Increasing inspiratory airway obstruction in croup (croup score  $\geq 4$  (32), see Table 2) should be managed by tracheobronchial administration of an aerosolized vasoconstrictor, e.g., epinephrine, using powered nebulizers or intermittent positive-pressure breathing devices (32,46). The need for an artificial tracheal airway in croup may be significantly reduced by early aerosolized administration of racemic epinephrine (61,62). As clinical improvement of croup after aerosol therapy may be transient, and additional treatments may be required, hospitalization is recommended for at least 24 hours after the last breathing treatment (32).

### Airway Management of Croup

Unlike airway indications in epiglottitis, the indications for an artificial airway in croup are not well defined. A worsening clinical picture refractory to medical management with aerosolized epinephrine and possibly steroids, an increasing croup score (32) ( $\geq 7$ , Table 2), a rising  $\text{PaCO}_2$ , and hypoxemia despite high inspired  $\text{O}_2$  concentrations will necessitate tracheal intubation. The choice between a translaryngeal (orotracheal tube, nasotracheal tube) or transtracheal (tracheostomy) airway in croup is also controversial. Some groups recommend tracheostomy in croup because of previous experiences with postintubation subglottic stenosis from endotracheal tubes (63,64). Certainly there are increased risks when placing a foreign body such as an endotracheal tube in an already inflamed larynx and subglottic trachea (32). Other experienced groups have reported a low incidence of airway complications, and recommend nasotracheal intubation for airway intervention in croup (52,53,65).



If endotracheal intubation is selected in managing severe croup, smaller than age-predicted endotracheal tubes (57), early extubation, and conversion to tracheostomy if prolonged intubation seems likely are highly recommended. Conscious or anesthetized tracheal intubation for severe croup can be accomplished in the same manner as recommended for epiglottitis, without the added need of avoiding epiglottic contact and suspension at laryngoscopy. As Downes has stressed, the major issue in managing airway obstruction in croup is not the type of tracheal airway selected, but rather the rapidity of establishing diagnosis, adequacy of initial treatment, careful insertion of the airway by experienced physicians, and meticulous respiratory care during and after intubation (32).

Criteria for extubation in croup include improving clinical picture, normalization of arterial blood gases, decreasing O<sub>2</sub> requirements, adequate hydration, and absence of significant associated pulmonary findings. As noted, early extubation with continuing aerosol treatments, or conversion of translaryngeal to trans-tracheal airway is preferable to prolonged endotracheal intubation in croup. Subglottic stenosis is a tragic sequel to airway intervention in croup, and is difficult to treat.

### Other Manifestations of Croup and Epiglottitis

Other manifestations of croup and epiglottitis appear mostly confined to pulmonary infiltrates and effusions, with right upper lobe infiltrates predominating in epiglottitis (15). Noncardiogenic pulmonary edema may occur from an obstructed extrathoracic airway in croup and epiglottitis as a result of alveolar hypoxia, increased capillary transmural pressures, and pulmonary venous congestion (66-68). Increased pulmonary vascular resistance with right ventricular enlargement, and increased systemic vascular resistance with reduced stroke volume may also occur with airway obstruction, reducing cardiac contractility and contributing to cardiogenic pulmonary edema (69). Positive pressure ventilation, diuretics, and colloid infusions may be necessary in addition to relief of airway obstruction in persistent pleural effusions associated with croup or epiglottitis (66). Cervical lymphadenopathy is common in epiglottitis, and may also occur in croup (14). Though systemic bacteremia occurs in nearly half of all cases of epiglottitis, such metastatic complications as septic arthritis, meningitis, pericarditis, and endocarditis are rare (14). Exudative tonsillitis, uvulitis, and otitis media may also complicate epiglottitis (2,14). Lumbar puncture is not routinely indicated in acute epiglottitis, but should be

carried out promptly to evaluate meningeal signs or persistent fevers in both patients and household contacts (24).

### Conclusions

In conclusion, the clinical presentations of severe croup and acute epiglottitis may overlap and lead to uncertainty. Croup is a common viral upper respiratory illness in infants and children that generally responds to hydration and humidification. Croup may occasionally cause more severe subglottic airway obstruction that, unlike epiglottitis, usually responds to combinations of oxygen therapy and aerosolized epinephrine. If artificial airway intervention becomes necessary in croup (Table 2), short-term nasotracheal intubation or tracheostomy is indicated. On the other hand, epiglottitis is an uncommon bacterial infection in children, rarely seen in adults, that produces immediate and life-threatening supraglottic airway obstruction. Therapy must be instituted swiftly and consists of oxygenation, antibiotic coverage, and an artificial tracheal airway to bypass short-term supraglottic obstruction.

Although croup is the most common infectious cause of acute upper airway obstruction in children, epiglottitis must be ruled out quickly in a child with airway obstruction. When equipment for tracheal intubation and ventilation is available, direct pharyngoscopy is a proven, safe, and reliable technique for early diagnosis of epiglottitis, when performed by experienced hands. Lateral neck films may prove valuable in evaluating subacute upper airway obstruction, but in suspected acute epiglottitis may waste precious time, interfere with protective posture, and divert interests away from relief of life-threatening airway obstruction. Optimal care involves attending physicians, anesthesiologists, and otolaryngologists linked in a team effort.

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## Technical Communications

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### Production and Characterization of Impurities in Isoflurane Vaporizers

Stephen T. Weldon, BS, Susan I. Williams-Van Alstyne, BSc, A. Jay Gandolfi, PhD, and Casey D. Blitt, MD

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Unwanted substances in hydrogenated anesthetics have been reported occasionally. Raventos and Lemon (1) and Torkelson et al. (2) characterized the toxicity of undesirable compounds found in halothane and methoxyflurane during their industrial synthesis. Their investigations led to an awareness of the possible impurities in anesthetics and steps were taken to improve the synthesis and stabilize the halogenated anesthetics. Current commercially available anesthetics are reported to contain less than .0075% wt/wt or less than 75 ppm impurities (1).

In a study by Sharp et al. (3), the breakdown of halothane during closed-circuit anesthesia was examined. The degradation was found to be due to the interaction of halothane with soda lime in the filtering unit. The product of this degradation, 2-bromo-2-chloro-1,1-difluorethylene is toxic (1). However, toxic concentrations did not accumulate during open- or closed-circuit anesthesia.

In 1981 Wald (4) described two instances of the presence of yellow "impurities" in enflurane in an Ohio calibrated vaporizer. Wald (4) felt that the impurities were not from the degradation of enflurane, but from a "sulfurous" paper component in the vaporizer wick. In 1982 we observed a yellowish discoloration in isoflurane in an Ohio calibrated vaporizer. Preliminary studies by our laboratory found that these impurities were not "sulfurous paper compo-

nents" but were organic in nature (5,6). This report characterizes the impurities in isoflurane vaporizers, determines their origin, and performs field analyses to determine the magnitude of the problem.

#### Methods

Samples of "contaminated" or discolored isoflurane were obtained from anesthetic vaporizers from the Arizona Health Sciences Center, Tucson Medical Center, and, via solicitation, from other hospitals throughout the United States. Additional discolored samples from isoflurane vaporizers were sent to us by Ohio Medical Products. All samples were stored in the dark at room temperature prior to analysis.

The 2,2-methylene-bis-(6-tert-butyl-p-cresol) (bisphenol) was obtained from Tokyo Kasei Chemical (Tokyo, Japan). The 2,4-dihydroxybenzophenone (benzoescorcinol) and diethylhexyl phthalate (DEHP) were purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI) and Supelco, Inc. (Bellefonte, PA), respectively. Isoflurane vaporizers, vaporizer parts, plastic wick spacers, and brass nuts were generously supplied by Ohio Medical Products, a division of Airco, Inc. (Madison, WI).

#### Analyses

**Absorbance.** Aliquots (0.1 ml) of each isoflurane sample were diluted to 1.0 ml with 100% ethanol and transferred to cuvettes. In a random analysis of the absorbance characteristics of the discolored isoflurane samples, a broad absorbance maximum at 459 nm was found. All subsequent samples were analyzed at 459 nm with a Beckman ACTA C-III Spectrophotometer (Fullerton, CA) as a measure of yellowish discoloration.

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**Residue.** Aliquots (1 ml) of each isoflurane sample were added to preweighed aluminum boats. After evaporation in a hood overnight, the boats were reweighed and the dry residue measured on a per ml basis.

**Gas chromatography/mass spectrometry (GC/MS).** Discolored isoflurane vaporizer samples (1–5 ml) were evaporated to dryness with a nitrogen gas flow and reconstituted in small volumes of ethanol. The solutions were injected in the gas chromatograph/mass spectrometer for analysis of constituents. A Finnegan 3300 gas chromatograph/mass spectrometer with NOVA 4 Data Base and Century Data System Disc Drive operating in the electron impact mode was used. The column for the gas chromatograph was a 180 cm  $\times$  2 mm inner diameter glass column packed with 3% OV-1 (100–120 mesh) with a helium carrier gas flow of 30 ml/min. The contaminants were eluted from the column by temperature programming. After injection, an initial temperature of 200°C was maintained for 1 min followed by a 15° C/min temperature increase to 290°C.

**Gas chromatography.** A Varian Instrument Model 3700 gas chromatograph equipped with a flame ionization detector was used for routine quantitation of impurities once their identity was confirmed by GC/MS and a suitable standard found. Separation of compounds was accomplished with a 50 cm  $\times$  3 mm internal diameter nickel column packed with 5% OV-101 on Chrom GHP (100–120 mesh). Injector port and detector temperatures were maintained at 250°C, and the column at 240°. Flow rates were 30 ml/min for nitrogen carrier gas, 30 ml/min for hydrogen, and 300 ml/min for air. Maximum sensitivity of the recorder was obtained through optimization of the electrometer range and attenuation. For the analysis, a 5- $\mu$ l sample of anesthetic from the vaporizer was injected on the column. A Varian CDS 111 integrator was used to measure the concentration of the impurities. Limits of detection were 1  $\mu$ g/ml. A 1 mg/ml standard of the previously described commercially obtained compounds was prepared for the gas chromatographic analyses. Serial dilutions were made to obtain the working standards in concentrations over the expected range. A linear regression analysis of the peak height versus concentration was used to calculate quantities in samples.

### *Vaporizer Study*

Three isoflurane vaporizers were filled with pure isoflurane (same lot) and examined for impurities. The vaporizers were identical except one had a plastic wick spacer, one had a brass wick spacer, and one had a

plastic wick spacer with brass retainer nuts lined with red nylon bushings. The anesthetic was vaporized, recondensed in a dry ice–acetone trap, recovered from the trap, and placed back in the reservoir of the respective vaporizer. This was repeated three times. From each vaporizer a sample of condensed anesthetic and reservoir liquid was removed and analyzed for impurities.

### *Vaporizer Component Study*

Plastic wick spacers and brass nuts with red nylon bushings were placed alone or in combination in separate 50-ml screw-cap tubes containing 25 ml of isoflurane. A control tube contained only isoflurane. The tubes were tightly capped, wrapped with foil and maintained at either 37° or 23°C. Aliquots (1 ml) were removed on subsequent days and analyzed for impurities.

### *Field Study*

In order to study the extent of the contamination, samples were obtained from the anesthetic vaporizers of the Arizona Health Sciences Center (Tucson, AZ) and Tucson Medical Center (AZ). Additional vaporizer samples were received courtesy of Ohio Medical Products (Murray Hill, NJ) and from individual anesthesiologists who requested that isoflurane from their vaporizer be analyzed for impurities. The vaporizer samples were assayed for residue weight, absorbance, and for specific impurities by gas chromatography. Specifically identified vaporizers from samples taken at the Arizona Health Science Center, Tucson Medical Center, and from unsolicited samples were grouped according to manufacturer.

## **Results**

### *GC/MS Structural Determinations*

Representative samples (1.5 ml) of discolored isoflurane obtained from an Ohio Medical Products isoflurane vaporizer were evaporated to dryness and introduced to the mass spectrometer via solid probe. One major component from the discolored residue was seen to desorb with heating with a mass-charge ion ratio of 340. By using the data base system of the mass spectrometer and via comparison to commercially available material, the fragmentation pattern was identified to belong to 2,2-methylene-bis-(6-tert-butyl-p-cresol) (Fig. 1). This compound was then routinely identified in isoflurane from vaporizers using

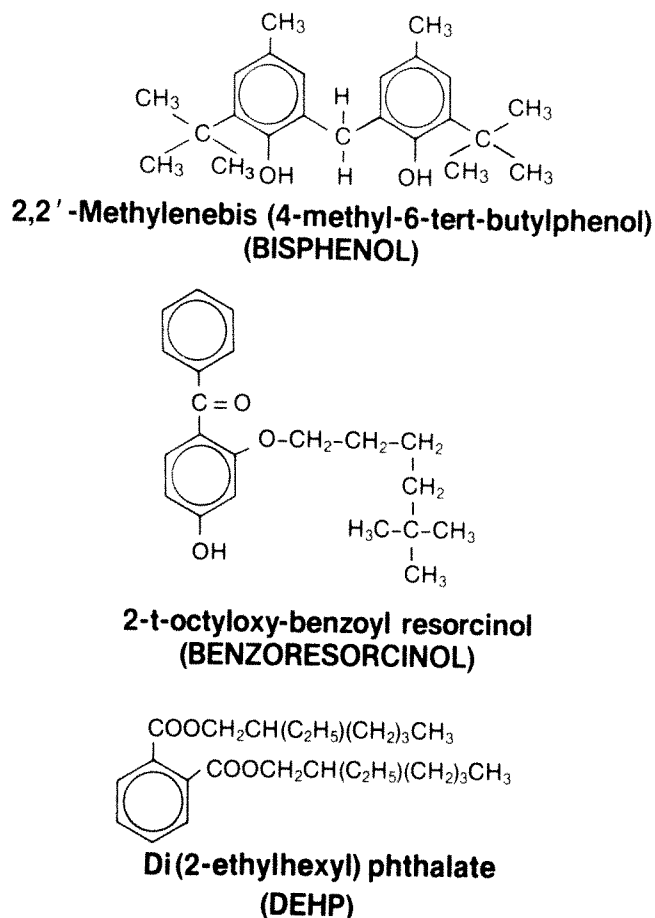


Figure 1. Structure of impurities in isoflurane vaporizers identified by gas chromatography/mass spectrometry.

a gas chromatographic technique and referred to as bisphenol (see methods section).

Subsequent analyses with combined GC/MS techniques identified two other substances in lesser quantities, diethylhexyl phthalate (DEHP) and 2-t-octyloxy-benzoyl resorcinol (benzoresorcinol) (Fig. 1). These substances could also be detected routinely by the gas chromatographic analysis for the bisphenolic compound. Retention time was found to be 1, 2, and 4 min for the bisphenol, DEHP, and benzoresorcinol, respectively. The isooctyl derivative of benzoresorcinol was not commercially available, so all analyses for that derivative are calculated using benzoresorcinol as the standard and are reported as benzoresorcinol equivalents.

#### Vaporizer Study

The vaporizer with no plastic components (brass wick spacer) did not produce discolored isoflurane in the reservoir during operation nor did it produce the pre-

viously identified major impurity, bisphenol (Table 1). However, when the brass wick spacer was replaced with a plastic wick spacer, the isoflurane did not discolor, but the bisphenol compound did appear in the isoflurane in the reservoir. When brass retainer nuts that contained red nylon bushings were also a component in the vaporizer, not only was the bisphenol present, but also the isoflurane in the vaporizer became discolored (Table 1). The content of DEHP and benzoresorcinol was not determined in these samples, because the assay for these compounds was not available during these studies.

#### Component Study

To specifically demonstrate the role of the plastic wick spacer and the brass retainer nuts with red nylon bushings in the contamination of the isoflurane vaporizers, the individual components and combinations were incubated with isoflurane. Isoflurane alone has no discoloration, dry residue, or contaminants. However, if the brass retainer nuts with red bushings are incubated with isoflurane, a dry residue is produced that does not have any discoloration. Additionally, if the plastic wick spacers are incubated with isoflurane, a dry residue is produced and the bisphenol contaminant is present in large quantities. Finally, if both the plastic wick spacers and the brass nuts with red nylon bushings are incubated together in isoflurane, not only are the bisphenol and dry residue present but also there is a yellow discoloration of the isoflurane (Table 2).

The production of the dry residue, bisphenol, and the discoloration was found to be dependent on the amount of plastic wick spacer and the brass nuts with red bushings. In addition, the rate of elution and production of the residue, impurities, and discoloration was directly dependent on the temperature of incubation.

#### Field Survey of Impurities in Isoflurane Vaporizers

Samples from Ohio Medical Products isoflurane vaporizers were obtained from local hospitals and from referrals by Ohio Medical Products and anesthesiologists (Table 3). They were analyzed for dry residue, yellow discoloration, and the impurities (bisphenol, DEHP, and benzoresorcinol).

All the vaporizer samples yielded a dry residue that is not present in pure isoflurane. The discoloration was most intense in samples referred to our laboratory by Ohio Medical Products and by concerned physicians. All the samples from these sources that were discolored had DEHP and benzoresorcinol present.

**Table 1.** Effect of Isoflurane Vaporizers Components on the Production of Impurities in Isoflurane

Differences in the isoflurane vaporizers	Time (hr) <sup>a</sup>	A <sub>459</sub> <sup>b</sup>	Bisphenol (μg/ml) <sup>c</sup>
Brass wick spacer	96	0	0
	168	0	0
	192	0	0
Plastic wick spacer	96	0	25
	168	0	46
	192	0	67
Plastic wick spacer	96	0.011	9
Brass nylon nuts	168	0.013	14
Red nylon bushings	192	0.019	14

<sup>a</sup>The vaporizers were operated as described in the methods and aliquots removed for analysis at these time points. All values are the mean of three analyses.

<sup>b</sup>Absorbance of a 0.1 ml aliquot diluted to 1 μl with ethanol.

<sup>c</sup>Bisphenol, 2,2-methylene-bis-(6-tert-butyl-p-cresol).

**Table 2.** Extraction and Formation of Impurities from Plastic Wick Spacers and Retainer Nuts Found in Isoflurane Vaporizers

Vaporizer Components <sup>a</sup>	A <sub>459</sub> <sup>b</sup>	Dry residue weight (mg/ml)	Bisphenol <sup>c</sup> (μg/ml)	DEHP <sup>d</sup> (μg/ml)	BR <sup>e</sup> (μg/ml)
Isoflurane alone	0.000	0.0	0	0	0
Red-bushing brass nuts	0.000	0.1	0	0	0
Plastic wick spacer	0.000	0.9	521	0	0
Plastic wick spacer with red-bushing brass nuts	0.145	1.0	851	4.6	9.5

<sup>a</sup>Components incubated with 24 ml of pure isoflurane at 37°C for 192 hr in the dark. All values are the mean of three analyses.

<sup>b</sup>Absorbance of 0.1 μl aliquot diluted to 1 ml with ethanol.

<sup>c</sup>Bisphenol, 2,2-methylene-bis-(6-tert-butyl-p-cresol).

<sup>d</sup>DEHP, diethylhexyl phthalate.

<sup>e</sup>BR, benzoescorcinol equivalents.

Due to the large sample groups, the average mean amount of impurities and discoloration do not readily reflect the occasional samples that were very discolored and contaminated with impurities. The rather high standard deviations indicate this variation.

#### *Effect of Vaporizer Manufacturer on Impurities in Isoflurane*

Samples referred to us by Ohio Medical Products and samples collected in our local hospitals were compared for amounts of impurities relative to the vaporizer manufacturer (Table 4). Only the Ohio Medical Products isoflurane vaporizers had any impurities and discoloration. All vaporizer samples, though, contained dry residue after evaporation.

#### **Discussion**

This is the first reported incidence of the modern halogenated inhalation anesthetics being contaminated by the vaporizing apparatus. Past concerns dealt with impurities present after synthesis, instability of the anesthetic to light, and degradation of the anes-

thetic by the soda lime carbon dioxide absorbing systems (1-3). The modern inhalation anesthetics are known for their chemical stability. In this report the anesthetic, isoflurane, is not degraded, but its interaction with plastic components within the vaporizer results in the extraction of chemicals and residue into the isoflurane resulting in a discoloration.

The identified impurities are all probable components used in the synthesis of different types of plastics. The bisphenol and benzoescorcinol compounds are both used in the mediation of the polymerization process. DEHP is added to plastics to make them more malleable. These components should not be expected to leach from the plastics in large quantities as long as the components are not exposed to an organic solvent. However, isoflurane, besides being an effective anesthetic, is also an excellent solvent. Thus the inclusion of plastic components in a vaporizer that utilizes isoflurane is inappropriate.

Our studies never truly identified the specific chemical structure or chemical complex responsible for the discoloration. From our evidence, though, the discoloration only occurred when the bisphenol was leached from the plastic wick spacers and the ben-

Table 3. Survey of Impurities in Isoflurane Vaporizers

Source <sup>a</sup>	n <sup>b</sup>	Dry residue ( $\mu\text{g/ml}$ )	A <sub>450</sub>	Bisphenol ( $\mu\text{g/ml}$ )	DEHP <sup>c</sup> ( $\mu\text{g/ml}$ )	Benzoresorcinol ( $\mu\text{g/ml}$ )
AHSC	22	0.78 $\pm$ 0.51	0	134 $\pm$ 191	0	0
TMC	34	0.48 $\pm$ 0.46	0.02 $\pm$ 0.02	11 $\pm$ 8	14 $\pm$ 23	1 $\pm$ 5
OHP	39	0.64 $\pm$ 0.36	0.10 $\pm$ 0.06	43 $\pm$ 57	29 $\pm$ 64	23 $\pm$ 22
OA	20	0.33 $\pm$ 0.41	0.03 $\pm$ 0.02	77 $\pm$ 145	41 $\pm$ 57	8 $\pm$ 7

<sup>a</sup>AHSC, Arizona Health Sciences Center; TMC, Tucson Medical Center; OHP, samples received from Ohio Medical Products; OA, other anesthesiologists who sent samples directly to us.

<sup>b</sup>n, number samples analyzed. Data presented as mean  $\pm$  SD.

<sup>c</sup>DEHP, diethylhexyl phthalate.

Table 4. Effect of Vaporizer Manufacturer on the Appearance of Impurities in Isoflurane

Vaporizer type	n	Dry residue (mg/ml)	A <sub>450</sub>	Bis-Phenol ( $\mu\text{g/ml}$ )	DEHP <sup>b</sup> ( $\mu\text{g/ml}$ )	Benzoresorcinol ( $\mu\text{g/ml}$ )
OHP <sup>a</sup>	34	0.71 $\pm$ 0.54	0.09 $\pm$ 0.06	12 $\pm$ 22	4 $\pm$ 16	1 $\pm$ 5
Others <sup>b</sup>	26	0.36 $\pm$ 0.32	0	0	0	0

<sup>a</sup>OHP, Ohio Medical Products.

<sup>b</sup>Others, Draeger, Foregger, Harris-Lake Vaporizers.

<sup>c</sup>DEHP, diethylhexyl phthalate.

zoresorcinol released from the brass retainer nuts with red bushings. The combination of these two components yields the yellow discoloration (Tables 1, 2). In preliminary studies, we found that we could discolor isoflurane by the addition of large quantities of benzoersorcinol alone. In the vaporizers the presence of the bisphenol may facilitate the formation of a discolored benzoersorcinol by the formation of a "chromophore complex." Further studies in this area were not attempted once the solution to the problem was found.

The possible intoxication of patients with these compounds is very remote. Only the bisphenolic compound was examined for its possible vaporization from the isoflurane vaporizer (6). Only very minute quantities were detected in vaporized isoflurane (less than 0.1  $\mu\text{g/ml}$  in recondensed isoflurane). In addition, the bisphenolic compound was not found toxic to mice at up to 3.2 g/kg (6). The toxicity of phthalate esters is known, but requires substantial quantities (7). The toxicity of the benzoersorcinol compound is not known, but we had no evidence for it being volatilized from the isoflurane vaporizer.

Only the vaporizers from Ohio Medical Products were found to contain the yellowish discoloration and the identified impurities (Table 4). The ubiquitous appearance of residue after evaporation of the isoflurane may result from the extraction of chemical impurities from the vaporizer components. We were amazed at the amount of particulate material present in some of the isoflurane samples collected from vaporizers at our local hospitals or sent to us from other concerned anesthesiologists. Visual examination of the particu-

late material identified them as hair-like fragments, particles of rubber rings or stoppers, and a cork-like substance among many other items.

The solution to the vaporizer impurities problem described in this study is simple. It appears that the plastic components within the Ohio Medical Products vaporizers are the source of the impurities. By replacing these parts with brass components the problem is solved. In fact, since the observation and examination of this problem, Ohio Medical Products has been systematically overhauling vaporizers containing the plastic components and replacing them with brass parts.

Considerable effort and a substantial portion of the cost of volatile anesthetics is expended in producing an ultrapure product. As with any drug, maximum purity is a prerequisite for any anesthetic agent. Isoflurane itself is an extremely pure and stable chemical. There is no published report indicating that it is ever degraded when handled properly. The sole culprit in this episode of anesthetic contamination was the delivery system. Fortunately, the impurities were not found to be vaporized by the anesthetic delivery system and were not found to be toxic.

Prior to marketing, exhaustive studies are performed to assure that the synthesized anesthetics are pure. However, little attention seems directed as to what actually comes out of the vaporizer. In this instance, discoloration was visually observed and led to the discovery of the impurities. One must ask just what impurities may go undetected because of no easily observable alteration of the anesthetic? In the future, the leaching of impurities into a volatile an-



esthetic and an examination of what is being delivered to the patient by the vaporizer should be considered as a standard test before the release of a new delivery system is allowed.

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## Effect of Temperature and Age on the Solubility of Enflurane, Halothane, Isoflurane, and Methoxyflurane in Human Blood

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The solubility of inhaled anesthetics in blood (i.e., the blood/gas partition coefficient) increases as the temperature of the blood decreases (1,2). Changes in temperature often accompany anesthesia and surgery. Because solubility influences uptake and the anesthetic partial pressure developed in the alveoli, changes in solubility caused by changes in temperature can influence the course of anesthesia.

The effect of temperature on the solubility of many modern anesthetics is known. However, such information is not currently available for the two newest agents, enflurane and isoflurane. The present report supplies that information and, in addition, reports values for halothane and methoxyflurane.

### Methods

With the approval of the University of California Committee on Human Research, we obtained 21 ml of venous blood from 18 healthy patients about to undergo surgery. Patients (mean  $\pm$  SD,  $47.4 \pm 17.6$  yr) were selected so that a range of ages (21–77 yr) might be examined. Blood samples were anticoagulated with EDTA. Hematocrit ranged from 36.6–48.5% (mean  $\pm$  SD,  $42.7 \pm 3.6\%$ ).

The blood from each patient was divided into three equal volumes, each of which was drawn into a 30-ml syringe. Twenty ml of a mixture of enflurane, isoflurane, halothane, and methoxyflurane vapor in air was added to each syringe. The concentration of each added gas was approximately 0.15 MAC. The syringes were maintained at 37, 30, or 22.5°C (one syringe at each temperature). Equilibration proceeded for approximately 2 hr, during which time the syringes were shaken at 15-min intervals. The gas phase then was analyzed by gas chromatography.

An aliquot (approximately 4 ml) of the blood from a given syringe was injected into an evacuated flask of known (measured) volume (approximately 600 ml). The flask was heated for approximately 5 min at 55–60°C and then returned to the temperature at which the syringe had been equilibrated. The flask was maintained at this temperature for 1.5 hr or longer and was shaken at 15-min intervals. Midway through this period, the pressure within the flask was brought to ambient pressure by the addition of ambient air. At the end of the period, 10 ml of air was added to the flask. Twenty ml of gas from within the flask was withdrawn and analyzed. For each subject, two determinations of solubility were made and averaged at each of the three temperatures.

The blood/gas partition coefficients were determined as follows:

$$[(V_f + 20 \text{ ml} - V_b)/V_b] [C_f/(C_s - C_f)],$$

where  $V_f$  is the volume of the flask;  $V_b$  is the volume of blood;  $C_f$  is the concentration of anesthetic in the gas phase of the flask; and  $C_s$  is the concentration of anesthetic in the gas phase of the syringe. Twenty ml are added to the numerator to account for the 20 ml of air added prior to removal of the sample for analysis. The subtraction of  $C_f$  from  $C_s$  in the denominator corrects for the anesthetic remaining in blood.

The average heat of solution in blood for each anesthetic was calculated for each subject using the following formula (3):

$$\text{Heat of solution} = \frac{2.3T_1T_2R}{(T_2 - T_1)} \cdot \log \frac{\lambda_2T_1}{\lambda_1T_2}$$

where  $T_1$  and  $T_2$  are the absolute temperatures at which the solubilities  $\lambda_1$  and  $\lambda_2$  were measured, and  $R$  is the gas constant (1.99 calories-mole<sup>-1</sup>-degree centigrade<sup>-1</sup>).

The percentage change in solubility per °C increase in temperature was calculated by taking the logarithm of the solubility values and performing linear regression analysis. Analysis of variance determined whether

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Table 1. Solubility and Heats of Solution of Four Anesthetics in Blood at Various Temperatures

	Isoflurane	Enflurane	Halothane	Methoxyflurane
Number of samples <sup>a</sup>	16	18	15	15
Blood/gas partition coefficient				
at 37°C	1.46 ± 0.09	2.11 ± 0.14	2.54 ± 0.18	15.44 ± 1.19
at 30°C	1.96 ± 0.10	2.96 ± 0.18	3.39 ± 0.26	21.25 ± 1.35
at 22°C	2.85 ± 0.24	4.43 ± 0.37	4.65 ± 0.39	32.29 ± 3.15
Slope (% change in solubility per °C increase)	- 4.36 ± 0.30	- 4.86 ± 0.32	- 3.96 ± 0.46 <sup>f</sup>	- 4.82 ± 0.45
Heat of solution (kcal·mole <sup>-1</sup> ·°C <sup>-1</sup> )	8.71 ± 0.14	9.69 ± 0.14	7.92 ± 0.24	9.57 ± 0.21

Values are given as the mean ± SD.

<sup>a</sup>For which complete data are available.

the change in solubility accompanying the change in temperature differed among the anesthetics. We then performed paired *t*-tests to determine the significance of differences among the anesthetic groups. We applied a Bonferroni correction (4) for multiple comparisons and accepted  $P < 0.01$  as representing statistical significance. We also tested whether the change in solubility accompanying the change in temperature was related to patient age (linear regression analysis).

## Results

As anticipated, solubility increased as the temperature decreased (Table 1). Also, the temperature-related changes in solubility differed among the anesthetics. Change was least with halothane, greater with isoflurane, and greatest with enflurane and methoxyflurane. The change for both halothane and isoflurane was significantly less than the change for enflurane or methoxyflurane ( $P < 0.001$ ). The difference between the data for halothane and those for isoflurane also reached significance ( $P < 0.01$ ). The difference between enflurane and methoxyflurane did not approach statistical significance. These findings were reflected in the differences found for the heats of solution. Heats of solution for each anesthetic differed from each other ( $P < 0.01$  to  $0.001$ ) except for enflurane and methoxyflurane. No correlation was found between temperature-related changes in solubility and either patient age (Figs. 1 and 2) or hematocrit.

## Discussion

Our values for the blood/gas partition coefficient at 37°C compare reasonably well with those previously determined (1,2), ours being on average slightly higher for each anesthetic. The greatest deviation from published values occurred for our determination of the

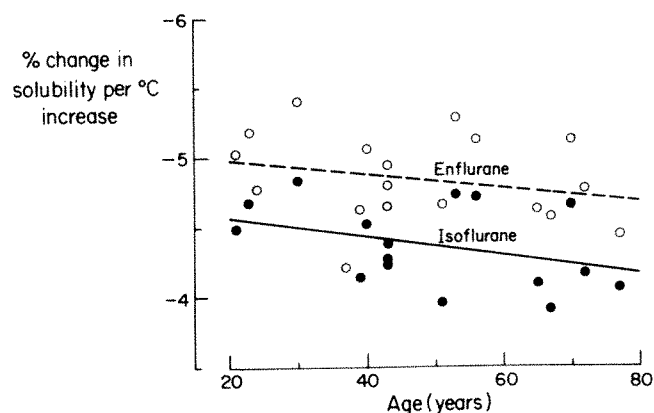


Figure 1. The change in solubility with temperature increases does not correlate significantly with patient age for either isoflurane (closed circles, continuous line) or enflurane (open circles, dashed line). The correlation coefficient is 0.38 for isoflurane and is 0.27 for enflurane.

solubility of methoxyflurane. Our value for methoxyflurane is approximately 20% higher than the average published values for methoxyflurane in human blood.

Similarly, values we obtained from published data for the effect of temperature on solubility are comparable to our values for halothane and methoxyflurane. For example, for halothane, our value of -3.96% change in solubility per °C increase in temperature is consistent with the following values we computed for data collected by other investigators: -4.22% [Han and Helrich (5)] and -3.84% [Lowe and Hagler (6)] for human blood, and -4.12% [Ikeda (7)] for canine blood. Similarly, our value of -4.82% for methoxyflurane agrees with the -4.75% value calculated from the data of Lowe and Hagler. It should be noted that the change in solubility per °C increase in temperature only applies to the range of temper-

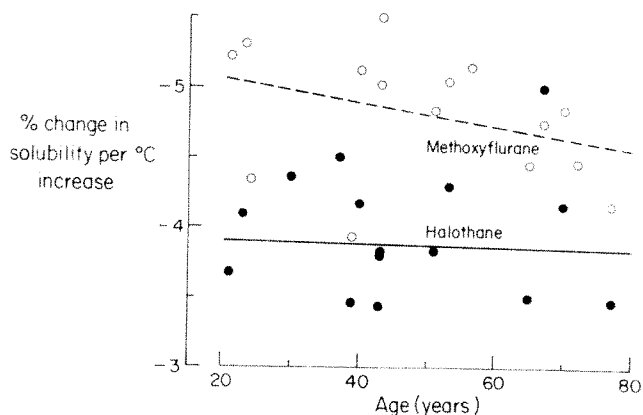


Figure 2. The decrease in solubility as temperature increases does not correlate significantly with patient age for either halothane (closed circles, continuous line) or methoxyflurane (open circles, dashed line). The correlation coefficient is  $-0.03$  for halothane and  $0.32$  for methoxyflurane.

atures studied. A deviation would be anticipated over a greater range.

The value for the change in solubility per  $^{\circ}\text{C}$  increase in temperature for isoflurane lies within the range of values provided by halothane at the lower extreme, and by methoxyflurane and enflurane at the upper extreme. Why differences exist among these anesthetics is not known. No correlation with the solubility of each anesthetic in hydrophobic or hydrophilic solvents (2) is apparent. Nonetheless, the finding that the heats of solution differed significantly among all anesthetics except enflurane and methoxyflurane indicates that the anesthetics interact differently with one or more components of human blood.

We have assumed that the presence of one anesthetic did not affect the solubility of the other anesthetics. This assumption is supported by the following reasoning. First, these vapors act as ideal gases even near their vapor pressures (8) and thus there is little likelihood of an interaction among the anesthetics. This likelihood is further decreased by the use of low concentrations (less than  $0.15$  MAC) for each agent in the determination of solubility. Second, as noted above, the solubilities we found are those previously found using only one agent, and are, if anything, slightly higher than other published values. Such findings rule out competition for solvent sites. Third, as noted above, the changes in solubility per degree change in temperature for halothane and methoxyflurane agree with previous estimates.

For all of the anesthetic agents studied, a decrease in temperature significantly increased solubility. Therefore, anesthetic uptake would be expected to increase significantly. The variation among anesthetics suggests that the effect of temperature on uptake would be greatest with enflurane and least with halothane. For example, a decrease from  $37^{\circ}\text{C}$  to  $30^{\circ}\text{C}$  would increase enflurane solubility by  $39\%$ , whereas the same change would increase halothane solubility  $31\%$ .

Our values for the percentage change in solubility per  $^{\circ}\text{C}$  increase in temperature apply to normal, healthy patients who have normal blood. The data do not allow us to predict the precise effect of changes in temperature on solubility of anesthetics when blood abnormalities such as anemia or hemodilution exist. We suspect that hemodilution would decrease the slope representing this relationship, because for many anesthetics, the slope for water or Krebs solution is less than that for blood (1,2,7,9,10).

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## Clinical Report

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### Methohexital Sedation of Children Undergoing CT Scan

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Computed tomography (CT) scans are performed frequently for the evaluation of central nervous system (CNS) pathology. The patient needs to remain relatively motionless for the duration of the scan, which is usually 15–30 min. Movement can produce artifact, which will make the scan nondiagnostic. Infants and young children are often unable to remain still for this period of time and hence require sedation or general anesthesia to maintain a motionless state. Delays caused by uncooperative children, or by prolonged induction of anesthesia represent a scheduling and economic burden to the radiology department as well as to the parents (1). In addition, many of these patients have repeated scans performed as outpatients, requiring the return to preanesthetic state as quickly as possible.

We evaluated the use of intramuscular methohexital for sedation of children undergoing CT scans of the head because complications such as respiratory depression, significant CNS depression, respiratory arrest (2), and failure to achieve a motionless state (3,4) are associated with other methods of sedation. Various concentrations of methohexital from 2 to 5% have been successfully used for sedation, although a 5% solution has been found to be less effective (5) than more dilute solutions. It is advantageous to use as small a volume as possible when employing the intramuscular route; therefore, we chose to compare two concentrations, 3.5 and 5%, of methohexital while giving the same dose per kilogram body weight to children undergoing CT scans of the head.

#### Methods

After approval by the Institutional Review Board and after parental consent, 50 consecutive patients, ages 2 months to 5 yr, scheduled to undergo a CT scan of the head received methohexital, 10 mg/kg, intramuscularly deep in the vastus lateralis muscle. The drug was administered by the anesthesiologist while the child was in his parent's lap. Once the child was asleep he was taken from his parent and placed in the CT scanner.

The children were randomly assigned to one of two groups: group A ( $n = 25$ ) received a 5% solution and group B ( $n = 25$ ) received a 3.5% solution. The methohexital was prepared by the pharmacist and supplied to the anesthesiologist in a coded syringe. Heart rate, blood pressure, respiratory rate, ECG, additional sedative requirements, and complications were monitored and recorded. After induction, intravenous catheters were inserted in those children requiring intravenous injections of contrast material for the scan ( $n = 39$ ).

The following times were recorded; time from methohexital injection until the patient was asleep and motionless sufficient to perform the scan; time from injection until the patient was arousable with stimulation; time from injection until the patient was fully awake with eyes open without stimulation. All children not awake at the end of the scan were observed in the recovery ward. The parents were contacted by telephone or postcard for follow-up information about local reactions at the injection site. Student's *t*-test was used to compare the results.

#### Results

Intramuscular methohexital alone provided adequate sedation to perform the scan in 46 of the 50 patients.

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**Table 1.** Sleep Times<sup>a</sup> Associated With Intramuscular Methohexital Administration

Group	Asleep	Arousable	Alert
A (5%)	3.3 ± 0.4	49.4 ± 7.0	87.4 ± 8.0
B (3.5%)	3.3 ± 0.4	44.6 ± 4.9	84.6 ± 6.6

<sup>a</sup>Mean ± SEM min.

In the 5% group one child received a total of 2.5 mg/kg of intravenous thiopental for hiccups, and in another child intravenous access for the injection of contrast material could not be secured before the child awakened from the drug. Two children in the 3.5% group were given incremental intravenous thiopental, a total of 2 mg/kg and 2.5 mg/kg, respectively, because of movement. One of these children was receiving chronic methylphenidate (Ritalin) therapy.

The mean times for each of the intervals measured are shown in Table 1. The average time from injection of methohexital until a motionless state was achieved was just over 3 min in both groups. Time until arousable with stimulation was approximately 50 min with the 5% solution (group A), and over 40 min with the 3.5% solution (group B). In both groups, the children were awake and alert in a mean time of 86 min. There were no statistically significant differences ( $P \geq 0.05$ ) for any of the times compared.

Because there were no significant differences between the two groups, we compared the nine children taking phenobarbital chronically to the remaining 41 children (Table 2). The times for these two groups were not statistically significantly different ( $P \geq 0.05$ ).

The methohexital solutions were prepared with sterile saline. The pH of both the 3.5 and 5% solution was 8.91. The osmolality of the 5% solution was 414 mOsm, and the 3.5% solution had an osmolality of 288 mOsm (Table 3).

There were no episodes of apnea, seizure, cyanosis, vomiting, voiding difficulties, or local reaction at the injection site. However, the injection was painful, because all children cried, even though only briefly.

## Discussion

Children and infants undergoing CT scans, especially as outpatients, require sedation that is safe, rapid in onset, and of short duration. Because valuable time and resources are lost when a child is uncooperative or motion artifact renders the scan nondiagnostic, the technique should also be able to predictably produce a motionless state.

We found that intramuscularly administered methohexital (10 mg/kg) produced adequate sedation and

**Table 2.** Sleep Times<sup>a</sup> of Children With and Without Chronic Phenobarbital Medication

Group	Asleep	Arousable	Alert
Phenobarbital ( <i>n</i> = 9)	2.7 ± 0.4	59.9 ± 16.8	82.6 ± 15.2
No phenobarbital ( <i>n</i> = 40)	3.6 ± 0.3	44.6 ± 3.6	86.6 ± 5.3

<sup>a</sup>Mean ± SEM min.

a motionless state sufficient to perform the scan in a mean time of just over 3 min. The methohexital alone provided adequate conditions for the scan in 92% of the patients. One CT scan was cancelled because intravenous access for administration of contrast material could not be obtained, and three children (6%) required additional sedation to achieve a motionless state. No studies were determined to be nondiagnostic due to motion. The average time until alert without stimulation was 86 min. There were no differences in the times for children receiving chronic phenobarbital therapy, and hence no need to alter the dosage in this group of children. The 5% solution was as effective as the 3.5%, indicating the smaller volume of methohexital can be used. There were no episodes of apnea, cyanosis, vomiting, voiding difficulties, or local reaction at the injection site.

Other methods of sedation have been associated with prolonged induction and recovery times, as well as failure to achieve a motionless state. Thompson, et al. (3), reported the average times until sedated sufficient to perform the scan with either oral chloral hydrate (80 mg/kg) or intramuscular mixture of atropine (.016 mg/kg), meperidine (1 mg/kg), promethazine (1 mg/kg), and secobarbital (4 mg/kg) at 55 min and 53 min, respectively. However, 10.5% of the patients in both groups required additional sedation, and in 15% of the patients given chloral hydrate and in 12% given the intramuscular mixture of drugs, the CT scan was unsatisfactory because it was not optimal for interpretation, or an intravenous line was not present to administer contrast material. Burckart et al (4), reported a nondiagnostic CT in 14% of children receiving an intramuscular mixture of meperidine (2 mg/kg), chlorpromazine (1 mg/kg), and promethazine (1 mg/kg), commonly referred to as DPT. In the same study (4), rectal thiopental in a dose of 25–45 mg/kg was associated with the need for additional sedation in 22% of the patients. The mean duration of sedation until the child was fully awake was 165 min for the rectal thiopental 25 mg/kg dose, and 7 hr for the intramuscular DPT group. These times compare to an average time of 86 min until fully alert after intramuscular methohexital.

Table 3. Osmolality (mOsm) and pH of Methohexital Solutions

Solution	Osmolality	pH
5%	414	8.91
3.5%	288	8.91

Many physicians caring for pediatric patients attempt to avoid intramuscular injections. Liu et al. (6), in their study of rectally administered methohexital for preoperative sedation of children, did not comment on patient acceptance, but the occurrence of defecation in 13% of the children was described as a shortcoming of the technique. Burckart et al. found that patient responses to rectal and intramuscular administrations were similar, with equal numbers of children in each group described as definitely combative (4). The reliability and safety of intramuscular methohexital make it our method of choice.

Methohexital has been reported both to cause (7) and to be unassociated (8) with seizures. EEG activity was not recorded during our study, but there was no clinical evidence of seizures in any of our patients. We feel it is reasonable to continue antiseizure medications up to the time of the scan, and found no need to alter the dose of methohexital in those children maintained on chronic phenobarbital therapy.

In conclusion, intramuscularly administered methohexital (10 mg/kg) produced rapid and reliable sedation of children undergoing CT scan of the head. There were no differences in any of the sleep times between the 5 and 3.5% groups. Children taking phenobarbital chronically did not have statistically

significant different sleep times as compared to the other children. There were no episodes of apnea, seizure, cyanosis, vomiting, voiding difficulties, or local reaction at the injection site in any of our patients. Although the injection of methohexital is associated with pain, this disadvantage is counterbalanced by its rapid onset and reliable action. Separation anxiety was minimized, and parental acceptance was very high. We conclude that intramuscular methohexital is a safe, effective, and short-acting means of sedating pediatric patients for CT scans.

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## Letters to the Editor

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### MAPP versus MAC

To the Editor:

It was interesting to read the recommendation by Drs. James and White (1) that the term MAC be replaced by MAPP. Their suggestion seems as reasonable as my earlier one in favor of MAP (2). Unfortunately, according to Professor Louis R. Orkin (personal communication) we are up against the human frailty of surgeons and others, who, on intimating a desire for more anesthetic, prefer to mutter "Hey, MAC" rather than "Hey, MAP (or MAPP)".

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### The 2-Chloroprocaine Test for Axillary Brachial Plexus

To the Editor:

There is need for a positive indicator of proper needle placement prior to injection of potentially cardiotoxic local anesthetic agents. Recent appreciation of potential cardiotoxicity of long-acting amide anesthetics increases the importance of proper needle placement in minimizing the incidence of systemic toxic reactions (1).

Successful performance of axillary block anesthesia using the sheath technique is dependent on accurate needle placement within the axillary sheath (2). I have found the 2-chloroprocaine test to be useful in preblock identification of proper needle placement in performing sheath/axillary blocks. The test dose provides a clear indicator prior to injecting the amide anesthetic agent. After placing the blunt needle, presumably within the sheath, I inject 8-10 ml of 3% 2-chloroprocaine. If the needle rests within the sheath, the patient experiences a change in sensation of the hand

in 2-4 min. If there is no sensory change in 4 min, I assume the needle is not in the sheath, and I then reinsert the needle and repeat the test dose of 2-chloroprocaine.

I have used this technique to identify successfully proper needle placement in performing sheath-axillary blocks in 30 patients for surgery on the wrist or hand. After injection with an amide anesthetic agent, anesthesia was satisfactory to complete the entire operation in 27 patients (90%). Two patients responded to a pinch with an Allis clamp at the time of incision. Their surgical procedures were completed without discomfort after injection of 2-4 ml of 1% lidocaine at the site of the incision and supplementary sedation. Both patients had a hand block at the end of surgery, suggesting that the needle had been within the sheath. One patient (3%), who had sustained a high velocity missile injury damaging his hand such that he was unable to distinguish a 2-chloroprocaine-induced paresthesia, required general anesthesia. Seven of the 30 patients required a repeat 2-chloroprocaine test. No signs of local anesthetic toxicity were observed.

The 2-chloroprocaine test requires no additional hardware or special technical facility. It is safe, easy to perform, should increase the success rate, and may prevent systemic toxic reactions. Prudence dictates that 2-chloroprocaine be injected not more than twice.

The 2-chloroprocaine test has been found to be a reliable test and should aid in identifying proper needle placement.

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### Monitoring the Processed EEG

To the Editor:

The article by Smith et al. (1) highlights some of the difficulties associated with the use of microprocessor-based in-



struments for the analysis of the EEG. The authors deal adequately with only few of these difficulties, however. To compare EEG patterns between patients, information is needed about patient age, arterial CO<sub>2</sub> tensions, and drug dosage, all of which have documented effects on the EEG (2-4). None of these data are provided by Smith et al. The information that is provided about the high- and low-pass filters is contradictory. In the methods section (p. 387), the low-pass filter is described as 1000 Hz with a Hewlett Packard strip chart recorder, but later in the discussion section (p. 391) a 30-Hz low-pass filter is described as being inserted before analysis to attenuate noise. EMG artifacts on the EEG occur mostly above 30 Hz, and the noise from the EMG could have been removed more appropriately by analyzing the frequency bands and excluding activity in the high frequencies, rather than the cumbersome and dubious subtraction process described. In fact, Sebel et al. (5) have demonstrated that the amplitude of cerebral electrical activity can increase after induction of anesthesia, with the loss of EMG activity (200-100 Hz), due entirely to increases in the slower delta (1-3 Hz) and theta (3.5-7.5 Hz) frequencies. Any subtraction of amplitude to produce a correction factor would yield negative values. The extra compensation for the change in anesthetic depth occurring during fentanyl and sufentanil anesthesia is insufficiently defined to distinguish it from the compensation for EMG artifact. The work of Sebel et al. (6) shows that the depressant effect of fentanyl on the EEG is completed within 2-3 min from the time of injection and, according to the induction protocol used by Smith et al., this would have been completed before the muscle relaxant was administered. Therefore the method of assessing the change in anesthetic depth during the onset of neuromuscular blockade requires expansion for constructive comment, but appears to be erroneous from the information available.

The authors refer to the thinning of the aperiodic analysis of the Neurometrics monitor that eliminates or modifies 75% of the presented waveforms from the EEG. Consequently, to comment in the discussion on the "increase in delta waves" and "decrease in the alpha and beta regions" suggests a similarity with the classical EEG that is no longer justified. The use of the amplitude and frequency of the fundamental wave with the Klein analyzer is not supported by any of the references that the authors cite, and by no work of which we are aware. Consequently the first differentiation (rate of change) and the second differentiation (acceleration) of these measurements are valueless, irrespective of how the numbers change during the procedures described.

We recommend the application of the statement of Grundy about sensory evoked potentials to the expanding field of EEG analysis: "The lack of generally accepted clinical protocols increases the difficulty of establishing new programs and hampers comparisons of results obtained in different institutions, impairing the objective assessment of this new technology" (7).

We believe that the establishment of mutually compatible standards would greatly enhance the clinical value of the application of this potentially life-saving technology.

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## In Response:

Thank you very much for allowing us to examine the letter submitted by Drs. Bolsin and Gillbe, concerning our article on EEG analysis during high-dose opiate anesthesia. Drs. Bolsin and Gillbe have brought up several interesting points, a few of which are pertinent. These are concentrated in the third sentence of the letter. Although we did not list the ages of individual patients, we did give a range of ages. Since the EEG data were not listed by individual patients, individual ages would probably not be useful. Drs. Bolsin and Gillbe are correct in implying that we should have given drug doses in the text, rather than asking the reader to dig that information out of a cited reference. The total doses before incision were morphine  $2.5 \pm 0.3$  mg/kg, fentanyl  $5.8 \pm 4.0$  mg/kg, and sufentanil  $9.1 \pm 1.0$  mg/kg.

Unfortunately, the rest of the letter is not nearly so well on target. Drs. Bolsin and Gillbe seem either to have misinterpreted the article or to have basically different assumptions from conventional ones about the processing of data and information. An example of the latter is seen in their statement that the information about the filters is contradictory. Actually, one should record data at a considerably broader frequency band (hence the 1K Hz filter) than that at which one analyzes them for recording and the 30 Hz filter for analysis. Otherwise, data are permanently lost due to the filtering process.

Bolsin and Gillbe then proceed with some contradictions of their own. They state that EMG artifact occurs mainly above 30 Hz and that our subtraction process was "cumbersome and dubious." They next quote Sebel et al. (1) as stating that EMG activity is between 200-100 Hz (sic). If this were true, then our 30 Hz filter would of course have eliminated the EMG noise. Their suggestion of "analyzing

frequency bands and excluding activity in the high frequencies" sounds suspiciously like the low-pass filtering that we did do as a preliminary step, only more cumbersome. Incidentally, Sebel et al. could not have stated that EMG activity was at 200–100 Hz on the basis of the cited article, since they used a 50-Hz low-pass filter for recording.

Bolsin and Gillbe are correct in stating that EEG amplitude increases during high-dose fentanyl, but they only obliquely implied that frequency decreases. In any case, two factors were simultaneously causing a change in the EEG numbers while the neuromuscular blockers were taking effect: continuation of the deepening of anesthesia and relatively rapid attenuation and elimination of muscle tremor. Inspection of Figure 2 in our article reveals that there were two slopes in the tracings: one due to anesthesia alone and a steeper one due to anesthesia plus muscle relaxant. Thus the change over time,  $t$ , just before the change to a steeper slope was subtracted from the change over time during the steeper slope. This is a simple process, and it would not yield "negative values," as inspection of Figure 2 reveals. No correction for changing anesthetic depth was necessary for morphine, since induction was so relatively slow. Inspection of Figures 3–13 reveals that the ultimate corrections and corrected baseline were similar for morphine (uncorrected for change in anesthetic depth) as for fentanyl or sufentanil (corrected for change in anesthetic depth), indirectly suggesting that the correction process for anesthetic depth was correct. As for the "insufficient definition" of the process, again, inspection of Figure 2 and the legend would clarify the method in less than a minute. We think that the correction method is clearly stated and is correct, and no evidence to the contrary has been presented in the above letter.

Bolsin and Gillbe then implied that since Sebel et al. (1) observed a complete EEG effect in 2–3 minutes, we should have, too. As clearly stated in our protocol, however, we performed a slow induction. Again, inspection of Figures 2, 3, and 12 demonstrate that the "completed depressant" effect of fentanyl or sufentanil required 10–18 min, not 2–3 min.

EMG activity does occur below 30 Hz, contrary to Drs. Bolsin's and Gillbe's statements. One can see this activity in the raw EEG and in the display processed by aperiodic analysis. More importantly, one can see this activity disappear within 2 min after injection of muscle relaxants. We have seen this phenomenon hundreds of times, in addition to the documentation in the 49 patients reported in the article under discussion. If Drs. Bolsin and Gillbe have a better explanation for the consistent disappearance of this activity after injection of muscle relaxants than its being EMG, we would be glad to hear it. None is stated in their letter, however.

Indirect evidence for the broad-spectrum contamination of the EEG by EMG activity comes from our unpublished spectral analysis of EMGs obtained from other parts of the body (eight muscle sites). It is consistently in the range of 5–300 Hz. (We used a 5-Hz high-pass filter for this preliminary analysis.) There is no reason to suppose that scalp muscles would behave differently.

Drs. Bolsin and Gillbe then state that because the waves are thinned, no comment can be made on changes in alpha waves, etc. Just because we counted about 250 waves/min, instead of about 1000 waves/min should not imply that we cannot discuss the classical waveforms. More than enough information remains to do just that. In addition, without thinning, the display would be unreadable. We suggest that Drs. Bolsin and Gillbe examine a display (3) before drawing hasty conclusions about what information can be derived from this technique.

The letter is not clear as to the type of "lack of support" regarding the Klein analyzer—mathematical, physical, physiological, or clinical. Notwithstanding, considerable physiological and clinical support is clearly documented in references 7 and 8 of our article. Several references giving mathematical support (Burch et al.) are in turn cited in these two references. Finally, regarding clinical support, our paper represents another step in that direction.

Regarding the latter, Drs. Bolsin and Gillbe make an interesting implication. They seem to imply that if no previous paper has appeared to "support" a system or method, it should not be used. If this were true, no initial work would get done, a condition counterproductive to science.

In conclusion, Drs. Bolsin and Gillbe have missed an important point. We are the first to attempt to compensate for the EMG-induced artifact that occurs during the awake state. We suggest that unless some type of correction or compensation is done, one should not accept as valid any claims concerning changes from awake values. Nor should one accept anesthetized values unless the authors have demonstrated that the EMG is not a contaminating factor—either with profound neuromuscular blockade or use of an independently displayed EMG, as we did with the Klein analyzer (Figure 2 in our paper).

We would agree that "generally accepted clinical protocols" would be ideal. The question arises, "Whose?" We are afraid that we would be wary of using those of Drs. Bolsin and Gillbe, given the carelessness and fuzzy character of the above letter.

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## Hypoxemia during Cardiopulmonary Bypass from Leaks in the Gas Supply System

To the Editor:

Disposable bubble oxygenators are efficient gas and heat exchangers, are associated with acceptable low levels of trauma to blood, and permit use of low ratios between gas flow and blood flow (1-3). The Shiley S100A oxygenator functions well at gas flow-to-blood flow ratios as low as 0.6 (3). Recently, however, three of our patients required inordinately high gas flows to maintain adequate arterial oxygen tensions ( $\text{PaO}_2$ ) during cardiopulmonary bypass (CPB) when the Shiley oxygenator was used. The problem proved to be leaks in the gas supply system.

### Case 1

A 47-yr-old man was having coronary artery bypass graft (CABG) surgery that was uneventful until shortly after CPB was initiated, when an arterial blood gas measurement (ABG) showed hypoxemia (Table 1). At that time, the in-line enflurane vaporizer going to the oxygenator was off. Oxygenation improved after the gas flow was increased and the enflurane vaporizer was replaced.

### Case 2

A 62-yr-old man was having mitral valve replacement that was uneventful until the blood in the arterial infusion line appeared dark shortly after CPB was started. Table 1 shows the initial arterial gas tensions during CPB and the improvement in oxygenation after the vaporizer was excluded (inset, Fig. 1).

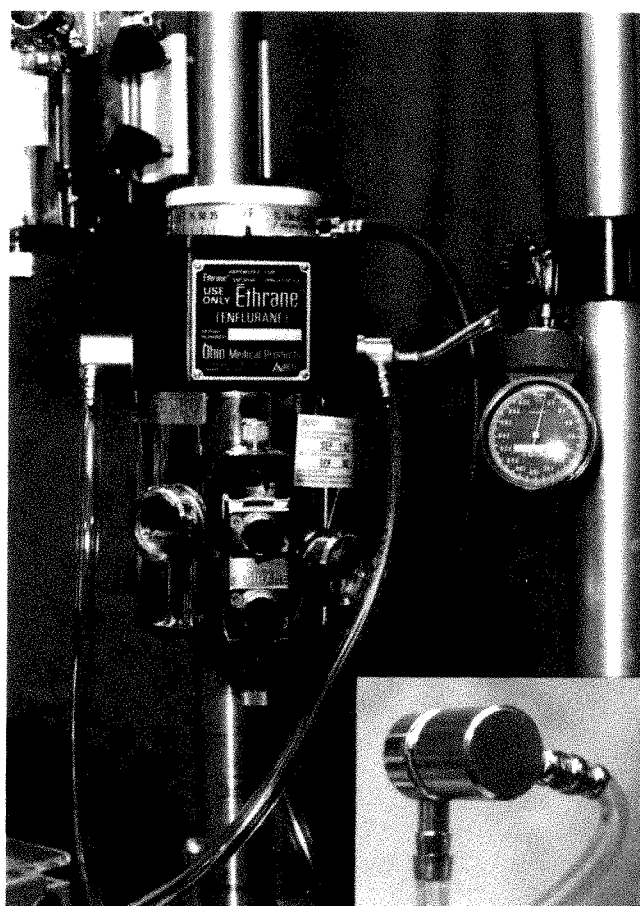
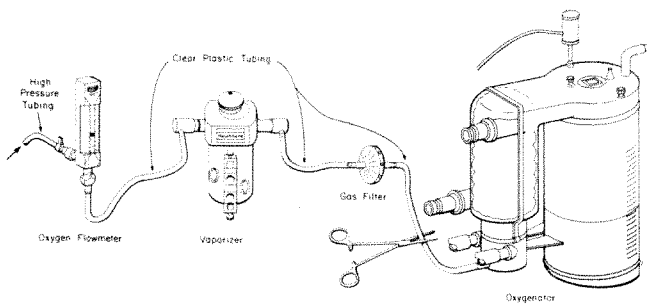


Figure 1. Enflurane vaporizer with clear plastic tubings leading to and from friction-seal metal adapters at gas inlet and outlet. Metal adapter attached to vaporizer outlet has been modified to accommodate an aneroid manometer used for low-pressure leak check. Inset shows two metal adapters used to bypass the vaporizer because of suspected leak.

Table 1. Intraoperative Variables during Normothermic CPB with Faulty Gas Supply Systems

Variable	Case Number					
	1		2		3	
	During hypox <sup>a</sup>	After hypox <sup>a</sup>	During hypox <sup>a</sup>	After hypox <sup>a</sup>	During hypox <sup>a</sup>	After hypox <sup>a</sup>
$\text{PaO}_2$ (mm Hg)	82	308	47	178	70	272
$\text{PaCO}_2$ (mm Hg)	29	27	35	36	44	41
pH	7.59	7.59	7.41	7.39	7.35	7.37
Gas flow (L/min; 100% $\text{O}_2$ )	4	5	3	3	6	10
Blood flow						
(L/min)	6.0	6.0	3.8	3.8	4.5	4.5
(L/min/m <sup>2</sup> )	2.4	2.4	2.0	2.0	2.6	2.6
Gas flow-to-blood flow ratio	0.67	0.83	0.79	0.79	1.33	2.22
Intervention	increased gas flow; replaced vaporizer		excluded vaporizer		increased gas flow; changed $\text{O}_2$ filter	

<sup>a</sup>Hypoxemia [at initiation of CPB and after correction of leaks in oxygen supply system.]



**Figure 2.** Schematic diagram of gas supply system to bubble oxygenator. Surgical clamp is shown next to suggested occlusion site for the pre-CPB system leak check. Schematic does not show in-line aneroid manometer used in leak check procedure.

### Case 3

A 53-yr-old post-CABG man undergoing CABG developed hypoxemia shortly after initiation of CPB (Table 1). Shortly after arterial oxygenation was improved by an increase in gas flow, a crack was detected in the disposable gas filter. The filter was replaced, after which the  $\text{PaO}_2$  was 272 mm Hg with a gas flow-to-blood flow ratio of 2.22 and 276 mm Hg with a gas flow-to-blood flow ratio of 1.73.

Hypoxemia during CPB may result from inadequate oxygen supplied to the oxygenator (leaks or obstructions in the gas supply line) (4), from oxygenator failure, or from inadequate blood flows (5). Light anesthesia and inadequate muscle paralysis can also contribute to hypoxemia by permitting increased peripheral oxygen consumption.

The excellent gas exchange capability of the Shiley S100A bubble oxygenator at low gas flows increases risk of hypoxemia when a leak develops in the gas supply line between the oxygen flow meter and the oxygenator (Fig. 2). During normothermic CPB, the gas flow-to-blood flow ratios delivered ordinarily produce a  $\text{PaO}_2$  of 150–350 mm Hg and a  $\text{PaCO}_2$  of 35–40 mm Hg. Because  $\text{CO}_2$  diffuses more readily than  $\text{O}_2$  (6), a compromised gas supply will more frequently cause hypoxemia than hypercarbia.

In case 1, where leakage was localized to the enflurane vaporizer, the problem was resolved by replacement of the vaporizer, which subsequently was found to have worn gaskets and O-rings. In case 2, either manual tightening of the male-female friction seal vaporizer adapters or exclusion of the vaporizer (as was done) would have corrected the leak. These adapters may cause clinically significant leaks despite careful hand tightening, and they must often be tightened with a wrench.

Whenever a  $\text{PaCO}_2$  of less than 100 mm Hg is encountered at the start of CPB, we recommend repeating ABG measurements and increasing the gas flow rate immediately while awaiting the results. In addition, the perfusionist should monitor the color of the blood in the arterial infusion line and inspect the oxygenating column to ensure adequate foaming. If inadequate foaming occurs, the perfusionist should seek a gas leak by feeling for cool air along the air supply lines and around all connection points, replacing or tightening them as necessary.

Because leaks greater than 250 ml/min in the gas line supplying the Shiley S100A oxygenator may be clinically significant, we recommend testing for leaks before starting CPB. We do this by placing an aneroid manometer in series with the gas supply tubing (Fig. 1), clamping the tubing just proximal to the oxygenator connection terminus (Fig. 2), increasing the gas flow until the manometer reads 40 mm Hg, and reducing the gas flow to the level that maintains that pressure. This test should be performed sequentially with the vaporizer(s) turned off and on. For a leak greater than 250 ml/min that cannot be corrected by tightening connections, we recommend inspecting the system with soapy water to locate and correct the leak. We now use this simple procedure routinely before starting CPB.

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## Translaryngeal Guided Intubation

To the Editor:

We read with interest the correspondence of Dr. Tobias (1) regarding the use of a fiberoptic laryngoscope during retrograde tracheal intubation. Use of a retrograde wire as a guide for difficult tracheal intubation has been proved to be very useful (2,3) and sometimes lifesaving. Although this technique was described more than two decades ago (4) it has not yet gained wide clinical acceptance and many anesthesiologists are reluctant to utilize it.

The simplicity of the retrograde technique allows fast and safe intubation even by the inexperienced. However, as Dr. Tobias described, at times it can be difficult to advance the endotracheal tube beyond the point where the guide wire enters the larynx. The distance between this point and the vocal cords is only 1.0–1.3 cm in average adults (5). Therefore, the endotracheal tube may be displaced from the larynx when the guide is being removed. To overcome this problem, Dr. Tobias suggested use of a fiberoptic laryngoscope in conjunction with placement of a



retrograde wire. In this way, the fiberoptic tip can be advanced into the trachea before the guide wire thereby avoiding possible displacement of the tip of the endotracheal tube.

In the past few years we have used a well-lubricated ordinary suction catheter or a nasogastric tube for the same purpose. Because the tracheal tube is already in the larynx and thus visual identification of anatomy is not necessary, a fiberoptic laryngoscope is not needed (6). A fiberoptic laryngoscope is not always available when unexpected acute airway obstruction occurs.

This technique is commonly referred to as "retrograde intubation." Because the endotracheal tube is not inserted from below, although the guide wire is, it would be more appropriate to call this technique "translaryngeal guided intubation."

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## Tracheal Intubation—Blind But Not Mute

To the Editor:

A number of devices have been described to facilitate blind tracheal intubation in noisy surroundings and in patients with low respiratory flow rates, e.g., small children or heavily sedated adults, conditions that make it difficult to hear breath sounds through the tracheal tube. These devices thus assure proper placement of the tip of the tube just above the larynx (1-5). In a recent article, Patil et al. described a microphone-amplifier-headset combination to aid in blind intubation under such conditions (6).

I recommend a yet simpler and less expensive alternative from the "pre-tech" era. The "BAAM" (Beck airway airflow monitor) (Great Plains Ballistics, PO Box 16385, Lubbock, TX 79490; Fig. 1), is based on the Venturi principle and fits the standard 15-mm endotracheal tube connector (7). The minimal peak flow rate required to change a weak breath

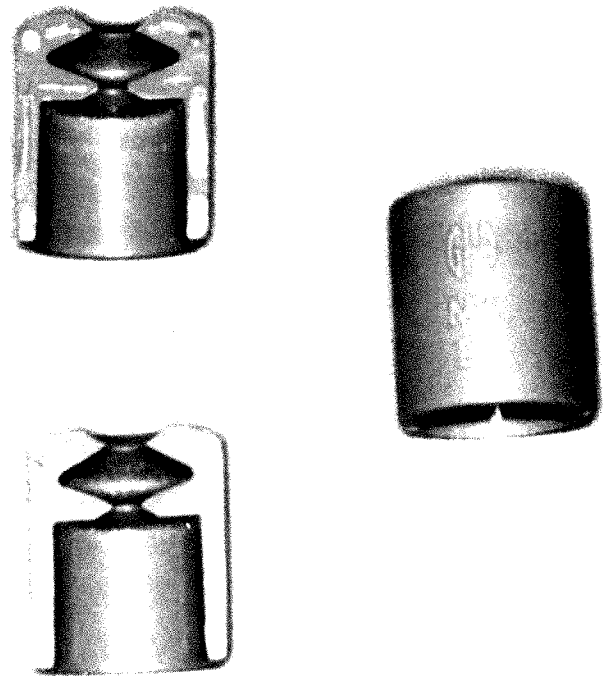


Figure 1. The Venturi chamber of the BAAM (reprinted with permission of the publisher of *Notfallmedizin* 1983;9:769-70).

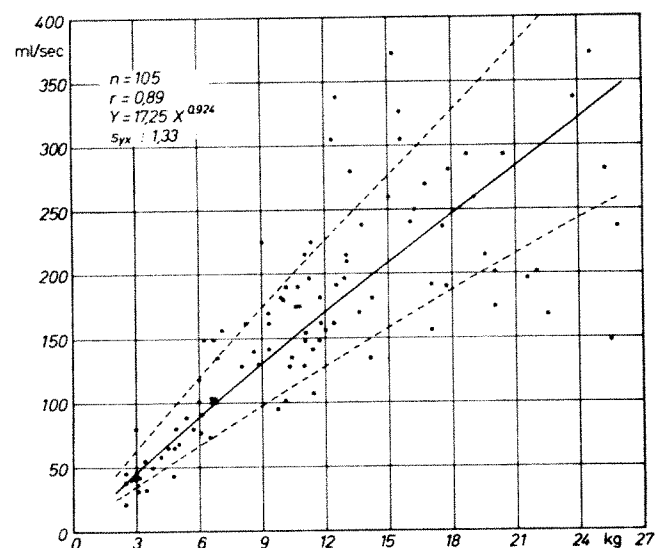


Figure 2. Maximal inspiratory flow rate and body weight (reprinted with permission of the publisher of *Anaesthesiologie und Wiederbelebung* 1967, vol. 24).

sound to a well audible whistle tone is only 50 ml/sec. Such a flow is present (Fig. 2) in anesthetized, spontaneously breathing children of 5-kg body weight (8).

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## An Unusual Source of Error

To the Editor:

The proliferation of monitoring equipment in the operating room and intensive care unit has at times led to an acute shortage of storage space. We recently noted difficulty in obtaining reliable cardiac output (CO) measurements due to the physical configuration of our equipment.

A 48-yr-old man required emergency exploratory laparotomy for acute small bowel obstruction. He had sustained three myocardial infarctions, had undergone coronary artery bypass surgery 7 yr prior to admission, and currently had angina at rest. Radial and pulmonary arterial monitoring were deemed necessary in addition to ECG and temperature. Room temperature saline solution 0.9% was used for thermodilution calculation of CO with an American Edwards thermodilution PA catheter model 93A-131-7F and a Sorenson model CO computer. The CO before induction of anesthesia was, on repeated determinations,  $2.2 \pm 0.4$  L/min despite a systemic blood pressure of 140 mm Hg and a pulmonary capillary wedge pressure (PCWP) of 14 mm Hg. Intravenous nitroglycerine (100  $\mu$ g/min) before induction did not affect the pressures or CO. The low CO and high systemic vascular resistance (2400) were attributed to anxiety and to the patient's past history of hypertension. After induction of anesthesia with thiopental 100 mg, fentanyl 15  $\mu$ g/kg, and tracheal intubation with vecuronium 0.1 mg/kg and cricoid pressure, the systemic blood pressure was 130 mm Hg and the PCWP 12 mm Hg; the CO remained in the 2.0-2.2 L/min range.

At this point, a sample of mixed venous blood from the pulmonary artery revealed an  $O_2$  saturation of 84%. This result seemed much more in accordance with the clinical situation than the CO. We then checked the injectate temperature measurement on the Sorenson CO computer, which read "30.1°C," much different than the room temperature of about 23°C. However, the injectate temperature probe was taped to our Dinamapp automatic sphygmomanometer (Fig. 1), which was warm to the touch. Replacement of the probe to the outside of the bag of flush solution caused the injectate temperature reading to decrease to 23°C, and the CO determination to increase to 5.5 L/min. The proximity



Figure 1. The arrangement of the cardiac output computer placed above the automatic sphygmomanometer, with the temperature probe of the computer inside a Vacutainer tube filled with saline, taped to the sphygmomanometer (arrow).

of the injectate temperature probe to the warm automatic sphygmomanometer gave a falsely elevated injectate sample temperature. Because the bolus of saline injected was colder than the sample temperature, the washout of cold saline took longer than it would have if the injectate temperature and the sample temperature had been the same. The slow washout made the CO appear lower than it actually was.

The measurement of CO by thermodilution was described by Fegler in 1957 (1). The volume of injectate and the temperature are co-related determinants of the accuracy of the measurement; a bolus of cold solution with enough caloric difference from the body temperature must be injected to give a reliable measurement of change in temperature (2). Civetta stated that "even a 1° difference in sampling between the actual 'room temperature of the injectate solution' and the sample medium of the injectate probe could introduce a 25% error in CO" (3). The difference between our actual injectate and the injectate probe warmed by the Dinamapp was 7.1°C.

Although space may be at a premium on the anesthesia machine, it is important to keep CO computer injectate probes away from warm monitoring devices.

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## Trigeminal Nerve Palsy after Lumbar Epidural Anesthesia

To the Editor:

Epidural anesthesia is a safe and useful method to control pain, but it is not completely free of complications. A patient was treated using this method and we experienced a rare complication, that, although already published in Japanese (Shigematsu S, Kobayashi M, Ochiai R, Nagano M. *The Journal of Pain Clinic* 1984;5(4):371-4), we feel deserves to be called to the attention of those who do not read Japanese.

A patient with periarteritis nodosa and severe bilateral leg pain was referred to our pain clinic. Epidural block was performed through an indwelling catheter at the L3-4 level. Bupivacaine, 18 ml of 0.5% solution, was injected through this catheter, and analgesia to the T9 level was achieved successfully. When the second dose of the same agent was given the next day, analgesia was not achieved but a right sided Horner's syndrome, paresthesia of the C4 and C5 dermatome area of the right arm, and evidence of trigeminal nerve palsy consisting of paresthesia of the right side of the face and dysarthria of the right side of the tempero mandibular joint appeared. The area of the facial paresthesia was that innervated by the ophthalmic and maxillary branches of the trigeminal nerve, and dysarthria was due to the paralysis of the muscles of mastication that are innervated by

the motor (mandibular) branch of the trigeminal nerve. There was no change in the level of consciousness or dyspnea and the symptoms subsided after 20 to 30 min. Bupivacaine, 10 ml of 0.5% solution, was subsequently injected through the same catheter on the same day, but none of these symptoms appeared. An x-ray study using a contrast dye showed that the dye spread around the L3-4 level in the epidural space and no abnormality was disclosed.

A few cases of Horner's syndrome, but no case of trigeminal nerve palsy after epidural block have been reported previously. On approaching the nucleus about 50% of the trigeminal nerve fibers divide into ascending and descending branches. The descending fibers form the spinal tract of the trigeminal nerve, which descends into the upper cervical part of the spinal cord. Also, the nucleus of the spinal tract of the trigeminal nerve is continuous below with the substantia gelatinosa. This may explain the trigeminal nerve palsy after epidural block that occurred in our patient.

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## Book Reviews

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### The Year Book of Critical Care Medicine

Mark C. Rogers, ed. Chicago: Year Book Medical Publishers, 1984, 462 pp, \$39.95.

Critical care medicine is a "specialty" that transcends many medical disciplines. Any compendium in this field must, of necessity, appeal to a diverse audience (anesthesiologists, surgeons, internists, pediatricians, perhaps nurses, respiratory therapists, and bioengineers, to name but a few). In this respect, the editors succeed rather well, despite the fact that all have appointments in the Department of Anesthesiology at Johns Hopkins University. On occasion such tightly knit groups are parochial in espousing their institutional viewpoints, but I did not detect this problem in either the selection of abstracted articles or the carefully constructed and thoughtful editorial comments.

A total of 332 articles from 82 journals was selected and presented in 15 chapters, ranging from emergent care and trauma, through shock, hemodynamic support, pulmonary pathophysiology, ventilation methods, and nutrition, to socioeconomic and ethical issues. The latter chapter contains 30 abstracted articles with commentary, and it bears out my contention that this subject matter forms the meat of critical care in the 1980s.

The editor's professional bias sneaks through in two chapters (operative monitoring and anesthesiology), which may have limited appeal to specialists other than anesthesiologists and surgeons. I think, however, that one can justify inclusion of these sections. Internists and pediatricians often are asked to provide consultative services to patients undergoing anesthesia and surgery, and usually have little or no knowledge of what transpires in the operating room.

Editorial comments generally are well done, informative, and "pull no punches." At the same time they are down to earth and occasionally witty. I was intrigued to find that video games have been reported to induce seizures in patients with light-sensitive epilepsy, and that this problem "is obviously more serious than 'Pac-Man' tendonitis."

As with other entries in the *Year Book* series, the format and general appearance of this volume are excellent. Typographical errors virtually are nonexistent. One will not become an expert in critical care by reading the *Year Book of Critical Care Medicine*, but interested physicians certainly can use it as a point of departure for later, more in-depth review of a large number of clinically relevant subjects.

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### Plexus Anesthesia, Volume I, Perivascular Techniques of Brachial Plexus Block

Alon P. Winnie, MD, ed. Philadelphia: WB Saunders Company, 1983, 272 pp.

This is an utterly fantastic work in terms of the beauty of its illustrations. The quantity and quality of both artwork and photography are unparalleled by any other anesthesiology reference book available today. Complementing the above is a very readable text that closely follows the illustrations and leads one to feel that regional anesthesia of the brachial plexus ought to be duck soup. You are almost compelled to feel confident about a successful outcome for your next nerve block of the upper extremity. Slightly disconcerting is the fact that a more careful job of proofreading would have corrected the few but flagrant misspellings. They are more noticeable than usual in light of the overall quality, style, and class.

The chapter titled "Historical Considerations" is especially well done, and its completeness attests to Dr. Winnie's depth of study of the subject. Indeed the foundations of this book are exceptionally well laid from historical and developmental points of view. There is, however, a nagging concern for its anatomic accuracy. In fairness, this reviewer is at odds with Dr. Winnie concerning the reality and clinical implications of compartmentalization of the neurovascular bundle. This disagreement is briefly alluded to on p. 64, but the essence of his text and the illustrations is to perpetuate the concept of a single compartment or sheath. From that germ concept emanate other expressions that might be challenged, e.g., the "immobile needle," emphasis on success related to "volume" of injected agent, and obstruction of proximal spread of solution by the "head of the abducted humerus." Perhaps these are but variations in the practice of an art, but anatomy is certainly a key feature of any regional block, and it is critical to the author's proposed techniques. If the sheath is truly not as depicted, then numerous questions arise. Can one really define brachial plexus anesthesia with the almost mathematical precision of many of Dr. Winnie's proposed techniques?

Few, if any, will have the diligence to pursue this subject with the passion and effort of the author. He has completed an exemplary text and is to be commended not only for stirring up interest in regional anesthesia but also for gathering together an international team of editor, artist, and photographer to create a work that will indeed have international impact.

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## Manual of Anesthesia, Second Edition

John C. Snow, ed. Boston: Little, Brown and Company, 1982, 434 pp, \$15.95.

This manual is intended as a basic guide for clinical anesthesiologists, residents, nurse anesthetists, and medical students. This second edition has retained the format of its predecessor with the addition of two new chapters on blood-gas analysis and invasive hemodynamic monitoring. There are 44 chapters divided into two sections. The first part is devoted to general considerations and covers topics ranging from preoperative evaluation of the surgical patient and preanesthetic medication to general anesthesia and muscle relaxants. The second section deals with anesthetic problems specifically related to the various surgical subspecialties.

In the preface the author states that the current edition "contains the latest information on malignant hyperthermia, diabetes, glycopyrrolate, pyridostigmine, nitroprusside . . . and vitrectomy." Although there are a number of excellent chapters, there are many omissions and errors. For example, the chapter on muscle relaxants fails to mention metocurine and atracurium, does not provide suitable dosages for intubation, and lists *d*-tubocurarine as contraindicated in renal disease; the chapter on vasopressors and adrenergic blocking agents omits dobutamine; and the discussions of CPR and the treatment of cardiac arrhythmias do not conform to the recommendations of the American Heart Association Advanced Cardiac Life Support guidelines.

This book should aim to provide the anesthetist, and the house officer especially, with a pocket reference source for information on the basic tenets of anesthetic practice of anesthesia and for information and drug dosages not necessarily used in everyday practice. The concept of such a manual is excellent, but this one does not meet that objective. Medical students and incipient junior residents may use it as a general work. The senior house officer or fellow, however, will find it lacking as an adequate pocket reference.

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University of Pittsburgh School of Medicine  
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## Understanding Anesthesia Equipment (second ed.)

by Jerry A. Dorsch and Susan E. Dorsch,  
Baltimore, Williams & Wilkins, 1984, 458 pp.

In order to provide a safe anesthesia experience for our patients it is imperative that we be familiar with the variety of equipment that they will encounter during an anesthetic. It has been reported that between 10–20% of errors during an anesthetic results from unfamiliarity with the equipment being used (1).

The second edition of the Dorsch's book provides useful information on most of the equipment in current use. The style is fairly uniform and for a technical book, it is surprisingly easy to read.

The chapter on vaporizers is particularly good and will be of benefit to every practitioner of anesthesia. All currently available vaporizers are discussed with regard to their construction, evaluation, and hazards. There are four chapters devoted to breathing systems. The first of these is clearly the best and includes a superb discussion of capnography and humidification. One of the chapters new to this edition is "Controlling Trace Gas Levels," an excellent review not only of the equipment involved, but the issue of occupational exposure in general.

A number of other chapters are not up to the quality of those just mentioned, but they in no way detract from the overall excellence of the book.

Many reviews end by recommending the book as an addition to one's library. The Dorsch's book should not be gathering dust in a library. It should be in the hands of every person administering anesthesia, and should be required reading before any trainee administers his or her first anesthetic.

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Children's Mercy Hospital  
Kansas City, MO 64108

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1. Cooper JB, Newbower RS, Long CD, McPeck B. Preventable anesthesia mishaps. *Anesthesiology* 1978;49:399–406.

## A Practice of Anaesthesia

Wylie and Churchill-Davidson, eds. Chicago: Year Book Medical Publishers, 1984, 1261 pp, \$89.95.

The first edition of this classic text on anesthesiology has undergone considerable revision from the previous one in terms of format (two columns), associate and assistant editors (four new editors), deletions and combinations of chapters, and addition of eight new chapters. The most extensive changes are the additional chapters on blood transfusion, anesthesia for obstetrics, oral and dental anesthesia, history, and anesthesia for special situations, including pediatric techniques. Two previous chapters on cardiac and circulatory complications and shock have been combined into a single chapter on circulatory arrest, and pulmonary and systemic embolism. Two chapters on the clinical use of neuromuscular blocking drugs, reversal agents, and factors affecting neuromuscular blockade replace a single chapter on cholinesterases and anticholinesterases.

The distinctly British origin of this text remains evident in terminology, drugs, and equipment used. However, the editors have attempted to provide both American and British viewpoints where differences or controversy exist. The clear, lucid British style is eminently readable. There are few misprints and little redundancy.

Particularly outstanding chapters include the entire section on the cardiovascular system and cardiopulmonary bypass and the discussion of neuromuscular blocking drugs and diseases affected by neuromuscular blockade. Parenteral nutrition, anaphylaxis, and therapy for tetanus are well

described in Chapter 10. The section on bronchography in Chapter 11 provides practical advice not available in other sources. Chapter 29 reviews the complications of anesthesia in an excellent fashion. Chapter 33 on pain clinics and regional blocks and Chapter 44 on special situations are concise and well organized.

The major drawbacks include the omission of detailed information on alfentanil, sufentanil, butorphanol, and nalbuphine, when nearly four pages are devoted to chloroform and there are extensive sections on diethyl and divinyl ether (including the open drop technique), trichloroethylene, and cyclopropane. Indeed, these sections are longer than those for halothane, enflurane, or isoflurane. There are detailed descriptions of other drugs unavailable in the United States. However, there is no information on the operation of either anesthetic or postoperative ventilators. The inclusion of a 30-page chapter on the history of anesthesia in a text of this type is unnecessary; a few historical facts incorporated into other chapters would be sufficient.

Chapter 8 on environmental hazards in the operating room fails to list hepatitis, AIDS, or other blood borne diseases as problems. Chapter 17 discusses Haemacel and Dextran, but not hetastarch, as plasma expanders. Chapter 35 on the liver indicates that hepatitis B vaccine is still undergoing trial, although it has been available in the US for more than two years.

As monitoring during anesthesia is generally less extensive in the UK than in the US, the limited discussions of pulmonary artery catheters, thermodilution cardiac output determinations, and mass spectrometers are understandable, but a definite disadvantage to the American trainee reader. Hemodynamic monitoring is presented primarily in the chapters on intensive care, with little mention of its usefulness intraoperatively.

All of these deficiencies, however, are relatively minor and overshadowed by the vast wealth of thoroughly researched and carefully written and edited information. As a classic text, this book continues to belong in the library of every student of anesthesia.

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### Books Received

Alfentanil—Pharmacology and Uses in Anaesthesia. Carl C. Hug Jr and Michael Chaffman. New Zealand: ADIS Press Limited, 1984, 115 pp.

Aids to Anesthesia—1. Basic Sciences. M.J. Harrison, T.E.J. Healy, and J.A. Thornton. New York: Churchill Livingstone, 1984, 238 pp, \$14.00.

Current Concepts in Regional Anaesthesia. J.W. Van Kleef, A.G.L. Burm, and J. Spierdijk. GR Dordrecht: Martinus Nijhoff Publishers, 1984, 252 pp, \$46.50.

Anesthetic Considerations in the Surgery of Atherosclerotic Cerebrovascular Disease. George P. Varkey. Boston: Little, Brown and Company, 1984, 205 pp, \$53.00 subscription per year.

Electrocardiography: Essentials of Interpretation. N. Goldschlager and M.J. Goldman. California: Lange Medical Publications, 1984, 236 pp, \$13.00.

Hypnotherapy of Pain in Children with Cancer. Josephine R. Hilgard. California: William Kaufmann, Inc., 1984, 250 pp, \$18.95.

Medical Abbreviations. Neil M. Davis. Pennsylvania: Neil M. Davis Associates, 1985, 61 pp, \$3.25.

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Anaesthesia Safety for All. Quintin J. Gomez, Lydia M. Egay, Merle F. dela Cruz-Odi. The Netherlands: Elsevier Safety Press B.V., 1984, 650 pp, \$130.75.

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**Prevent pain.  
Prolong analgesia.  
Promote early ambulation.**



PRESERVATIVE-FREE<sup>®</sup>  
**Duramorph<sup>®</sup> PF**  
(morphine sulfate injection, USP) CII

# creates new options in pain management

## 1 **DURAMORPH<sup>®</sup> PF provides profound site-selective analgesia.**

DURAMORPH<sup>®</sup> PF delivers preservative-free morphine directly to localized opiate receptors in the spinal cord, selectively blocking nociceptive impulse transmission to the brain's pain centers.

## 2 **DURAMORPH<sup>®</sup> PF prevents postoperative pain when administered at the completion of surgery.**

A single 5 mg epidural injection before the onset of postoperative pain provides pain relief associated with many obstetric/gynecologic, orthopedic, thoracic, and abdominal procedures. Use of DURAMORPH<sup>®</sup> PF is particularly convenient when an epidural catheter is already in place for operative anesthesia.

***“From a humanitarian viewpoint, epidural morphine could be considered the ideal postoperative analgesic . . .”***<sup>1</sup>

#### References:

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### **Guidelines for Administration of DURAMORPH<sup>®</sup> PF**

- The epidural route should be used whenever possible; intrathecal administration has been associated with greater potential for immediate or delayed adverse effects.
- Administration should be limited to the lumbar region whenever possible; thoracic injection has been shown to dramatically increase the incidence of respiratory depression.
- Predisposing factors in morphine-related respiratory depression include: thoracic administration,<sup>4</sup> advanced age,<sup>4</sup> reduced ventilatory capacity,<sup>5</sup> high doses,<sup>6</sup> concomitant administration of opioids,<sup>5</sup> supine body position,<sup>7</sup> CNS depressants,<sup>5</sup> and raised intrathoracic pressure.<sup>8</sup> Careful selection of patients, avoidance of opiate premedication, and maintenance of patients in a head-up position may minimize the occurrence of respiratory depression.

**See complete prescribing information**



### **3** DURAMORPH® PF relieves pain for up to 24 hours with a single epidural injection.

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DURAMORPH® PF provides extended pain protection with a duration of analgesic effect that is nearly four times longer than that of conventional systemic narcotics (IV morphine).<sup>1</sup>

### **4** DURAMORPH® PF is associated with a low incidence of respiratory depression.

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Delayed respiratory depression has been reported; patient monitoring should be continued for at least 24 hours after each dose. Naloxone reverses respiratory depression without diminishing analgesia.

### **5** DURAMORPH® PF maintains patient comfort with virtually no sedation, or loss of motor or sympathetic function.

---

DURAMORPH® PF out-performs conventional systemic narcotics and local anesthetics in producing site-selective analgesia. Patients are alert and more active participants in their nursing and rehabilitative care.

### **6** DURAMORPH® PF promotes early ambulation and reduces postoperative complications.

---

Patients receiving DURAMORPH® PF frequently become ambulatory earlier than patients receiving conventional systemic narcotics—often in as little as half the time<sup>1</sup>—which may reduce the risk of postoperative respiratory and thromboembolic complications.<sup>3</sup>

***“Due to absence of sedation and the lack of orthostatic hypotension, high risk patients . . . ambulate early leading to decreased risk for postoperative thromboembolic and respiratory complications.”<sup>2</sup>***

### **7** DURAMORPH® PF may hasten patient recovery and shorten hospital stays.

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In a study of patients at high risk of postoperative complications, epidural morphine shortened hospital stays after elective gastropasty from an average of 9 days to 7 days.<sup>3</sup>

### **8** DURAMORPH® PF may mean cost savings in postoperative care.

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The benefits of early ambulation, greater patient cooperation with nursing/rehabilitative care, fewer postoperative complications, and shortened hospital stays—offset against the moderately increased costs of short-term postoperative monitoring—may result in a significant net savings in the costs of medical care, an important consideration for institutions dependent on fixed-cost reimbursement policies.

***“... effective analgesia, early ambulation, early normalization of gastrointestinal function, and minimal respiratory complications in the postoperative period all contributed to a shorter hospitalization time in patients receiving epidural morphine analgesia.”<sup>3</sup>***

# PRESERVATIVE-FREE<sup>®</sup> Duramorph<sup>®</sup> PF (morphine sulfate injection, USP) CII

## DESCRIPTION

Preservative-free DURAMORPH<sup>®</sup> PF (Morphine Sulfate Injection, USP) is a sterile, pyrogen-free, isobaric solution free of antioxidants, preservatives or other potentially neurotoxic additives, and is intended for intravenous, epidural or intrathecal administration as a narcotic analgesic. Each milliliter contains morphine sulfate 0.5 mg or 1 mg (Warning: May Be Habit Forming) and sodium chloride 9 mg in Water for Injection, pH range is 2.5-6.0. Ampuls are sealed under nitrogen. Each Dosette<sup>®</sup> ampul is intended for SINGLE USE ONLY. Discard any unused portion. DO NOT AUTOCLAVE.

## INDICATIONS AND USAGE

Preservative-free DURAMORPH<sup>®</sup> PF is a systemic narcotic analgesic for administration by the intravenous, epidural or intrathecal routes. It is used for the management of pain not responsive to non-narcotic analgesics. Morphine sulfate, administered epidurally or intrathecally, provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.

## CONTRAINDICATIONS

DURAMORPH<sup>®</sup> PF is contraindicated in those medical conditions which would preclude the administration of opioids by the intravenous route—allergy to morphine or other opiates, acute bronchial asthma, upper airway obstruction.

Administration of morphine by the epidural or intrathecal route is contraindicated in the presence of infection at the injection site, anticoagulant therapy, bleeding diathesis, parenterally administered corticosteroids within a two week period or other concomitant drug therapy or medical condition which would contraindicate the technique of epidural or intrathecal analgesia.

## WARNINGS

DURAMORPH<sup>®</sup> PF administration should be limited to use by those familiar with the management of respiratory depression, and in the case of epidural or intrathecal administration, familiar with the techniques and patient management problems associated with epidural or intrathecal drug administration. Because epidural administration has been associated with lessened potential for immediate or late adverse effects than intrathecal administration, the epidural route should be used whenever possible. Rapid intravenous administration may result in chest wall rigidity.

FACILITIES WHERE DURAMORPH<sup>®</sup> PF IS ADMINISTERED MUST BE EQUIPPED WITH RESUSCITATIVE EQUIPMENT, OXYGEN, NALOXONE INJECTION, AND OTHER RESUSCITATIVE DRUGS. WHEN THE EPIDURAL OR INTRATHECAL ROUTE OF ADMINISTRATION IS EMPLOYED, PATIENTS MUST BE OBSERVED IN A FULLY EQUIPPED AND STAFFED ENVIRONMENT FOR AT LEAST 24 HOURS.

SEVERE RESPIRATORY DEPRESSION UP TO 24 HOURS FOLLOWING EPIDURAL OR INTRATHECAL ADMINISTRATION HAS BEEN REPORTED.

Morphine sulfate may be habit forming. (See Drug Abuse and Dependence section.)

## PRECAUTIONS

### GENERAL

Preservative-free DURAMORPH<sup>®</sup> PF (Morphine Sulfate Injection, USP) should be administered with extreme caution in aged or debilitated patients, in the presence of increased intracranial/intraocular pressure and in patients with head injury. Pupillary changes (miosis) may obscure the course of intracranial pathology. Care is urged in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis). Seizures may result from high doses. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.

It is recommended that administration of DURAMORPH<sup>®</sup> PF by the epidural or intrathecal routes be limited to the lumbar area. Intrathecal use has been associated with a higher incidence of respiratory depression than epidural use.

Smooth muscle hypertonicity may result in biliary colic, difficulty in urination and possible urinary retention requiring catheterization. Consideration should be given to risks inherent in urethral catheterization, e.g., sepsis, when epidural or intrathecal administration is considered, especially in the perioperative period.

Elimination half-life may be prolonged in patients with reduced metabolic rates and with hepatic or renal dysfunction. Hence, care should be exercised in administering morphine in these conditions, particularly with repeated dosing.

Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be observed carefully for orthostatic hypotension, particularly in transport.

Patients with chronic obstructive pulmonary disease and patients with acute asthmatic attack may develop acute respiratory failure

with administration of morphine. Use in these patients should be reserved for those whose conditions require endotracheal intubation and respiratory support or control of ventilation.

## DRUG INTERACTIONS

Depressant effects of morphine are potentiated by either concomitant administration or in the presence of other CNS depressants such as alcohol, sedatives, antihistaminics or psychotropic drugs (e.g., MAO inhibitors, phenothiazines, butyrophenones and tricyclic antidepressants). Premedication or intra-anesthetic use of neuroleptics with morphine may increase the risk of respiratory depression.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**  
Studies of morphine sulfate in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

## PREGNANCY

**Teratogenic effects—Pregnancy Category C.** Animal reproduction studies have not been conducted with morphine sulfate. It is also not known whether morphine sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Morphine sulfate should be given to a pregnant woman only if clearly needed.

**Nonteratogenic effects.** Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

## LABOR AND DELIVERY

**Intravenous morphine** readily passes into the fetal circulation and may result in respiratory depression in the neonate. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the neonate. In addition, intravenous morphine may reduce the strength, duration and frequency of uterine contraction resulting in prolonged labor.

**Epidurally and intrathecally** administered morphine readily passes into the fetal circulation and may result in respiratory depression of the neonate. Controlled clinical studies have shown that epidural administration has little or no effect on the relief of labor pain.

However, studies have suggested that in most cases 0.2 to 1 mg of morphine intrathecally provides adequate pain relief with little effect on the duration of first stage labor. The second stage labor, though, may be prolonged if the parturient is not encouraged to bear down. A continuous intravenous infusion of naloxone, 0.6 mg/hr. for 24 hours after intrathecal injection may be employed to reduce the incidence of potential side effects.

## NURSING MOTHERS

Morphine is excreted in maternal milk. Effect on the nursing infant is not known.

## PEDIATRIC USE

Safety and effectiveness in children have not been established.

## ADVERSE REACTIONS

The most serious side effect is respiratory depression. Because of

delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing. Bolus administration by the epidural or intrathecal route may result in early respiratory depression due to direct venous redistribution of morphine to the respiratory centers in the brain. Late (up to 24 hours) onset of acute respiratory depression has been reported with administration by the epidural or intrathecal route and is believed to be the result of rostral spread. Reports of respiratory depression following intrathecal administration have been more frequent, but the dosage used in most of these cases has been considerably higher than that recommended. This depression may be severe and could require intervention (See Warnings and Overdose sections). Even without clinical evidence of ventilatory inadequacy, a diminished CO<sub>2</sub> ventilation response may be noted for up to 22 hours following epidural or intrathecal administration.

While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulating catecholamines. Excitation of the central nervous system resulting in convulsions may accompany high doses of morphine given intravenously. Dysphoric reactions may occur and toxic psychoses have been reported.

Epidural or intrathecal administration is accompanied by a high incidence of pruritus which is dose related but not confined to site of administration. Nausea and vomiting are frequently seen in patients following morphine administration. Urinary retention which may persist for 10-20 hours following single epidural or intrathecal administration has been reported in approximately 90% of males. Incidence is somewhat lower in females. Patients may require catheterization (see Precautions). Pruritus, nausea, vomiting and urinary retention frequently can be alleviated by the intravenous administration of low doses of naloxone (0.2 mg).

Tolerance and dependence to chronically administered morphine, by whatever route, is known to occur (see Drug Abuse and Dependence section).

Miscellaneous side effects include constipation, headache, anxiety, depression of cough reflex, interference with thermal regulation and oliguria. Evidence of histamine release such as urticaria, wheals and/or local tissue irritation may occur.

In general, side effects are amenable to reversal by narcotic antagonists. NALOXONE INJECTION AND RESUSCITATIVE EQUIPMENT SHOULD BE IMMEDIATELY AVAILABLE FOR ADMINISTRATION IN CASE OF LIFE-THREATENING OR INTOLERABLE SIDE EFFECTS.

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance:** Morphine sulfate is a Schedule II substance under the Drug Enforcement Administration classification.

**Abuse:** Morphine has recognized abuse potential.

**Dependence:** Cerebral and spinal receptors may develop tolerance/dependence independently, as a function of local dosage. Care must be taken to avert withdrawal in those patients who have been maintained on parenteral/oral narcotics when epidural or intrathecal administration is considered. Withdrawal may occur following chronic epidural or intrathecal administration, as well as the development of tolerance to morphine by these routes. (See Nonteratogenic effects under Pregnancy.)

## OVERDOSAGE

Overdosage is characterized by respiratory depression with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory center or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone, is a specific antidote. Naloxone (usually 0.4 mg) should be administered intravenously, simultaneously with respiratory resuscitation. As the duration of effect of naloxone is considerably shorter than that of epidural or intrathecal morphine, repeated administration may be necessary. Patients should be closely observed for evidence of renarcotization. *Note: Respiratory depression may be delayed in onset up to 24 hours following epidural or intrathecal administration.* In painful conditions, reversal of narcotic effect may result in acute onset of pain and release of catecholamines. Careful administration of naloxone may permit reversal of side effects without affecting analgesia. Parenteral administration of narcotics in patients receiving epidural or intrathecal morphine may result in overdosage.

## HOW SUPPLIED

Amber Dosette<sup>®</sup> ampuls for intravenous, epidural and intrathecal administration.

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Revised September 1984



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So, prevent minor procedures from becoming major hypoxic crises. Rely on the Ohmeda Biox 3700. It's the confident response to the critical demands of anesthesia.

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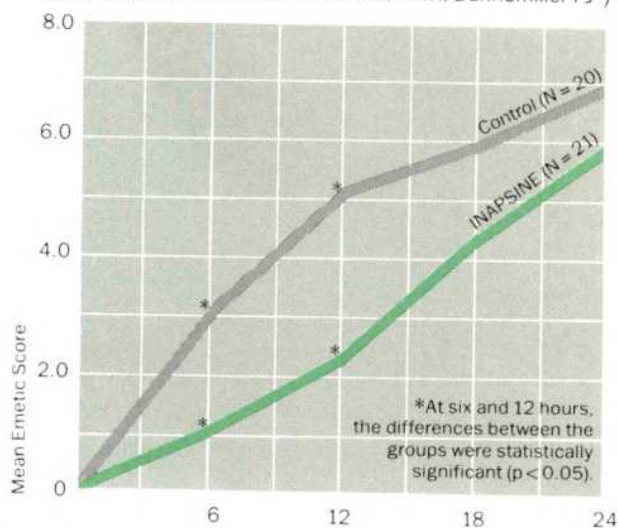
“...we found droperidol [INAPSINE®] to be a safe and effective prophylactic anti-emetic agent in this group of patients at high emetic risk.”<sup>①</sup>

# 1984:

“The incidence of postoperative nausea/vomiting... was higher in patients who received hydroxyzine as premedicant compared to those who received droperidol [INAPSINE] ( $p < 0.05$ ).”<sup>②</sup>

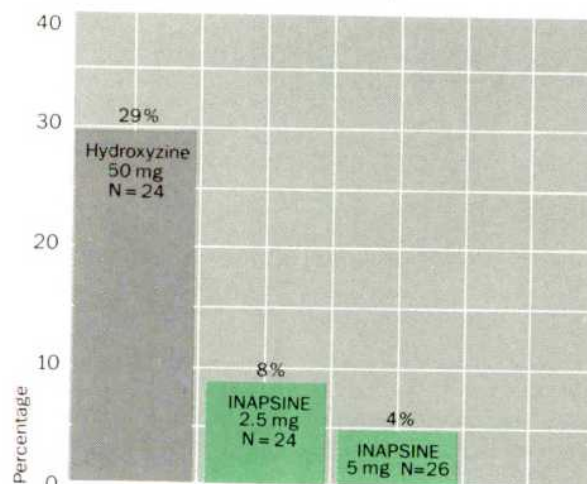
Double-blind study of 41 patients undergoing hysterectomy. Twenty-one patients received 5 mg INAPSINE shortly after surgery began, while 20 patients received placebo. Postoperative emesis was rated according to an emetic scoring system. Patients receiving INAPSINE had significantly less frequent and less severe nausea, retching and vomiting during the first 12 preoperative hours.

INAPSINE vs placebo: mean total emetic scores. The lower the score, the fewer and less severe the incidents of emesis. (Adapted from Patton CM Jr, Moon MR, Dannemiller FJ<sup>1</sup>)



Double-blind comparison of INAPSINE 5 mg, INAPSINE 2.5 mg and hydroxyzine 50 mg, combined with meperidine or morphine and glycopyrrolate, as premedication in 74 women undergoing major elective gynecologic surgery. Significantly fewer of the patients receiving INAPSINE experienced postoperative nausea/vomiting than those receiving hydroxyzine ( $p < 0.05$ ).

Percentage of patients experiencing postoperative nausea/vomiting according to premedication ( $p < 0.05$ ). (Based on Mehta P, Theriot E, Mehrotra D, et al<sup>2</sup>)



Before prescribing please consult complete prescribing information, of which the following is a brief summary. Protect from light. Store at room temperature. FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY. Droperidol is a neuroleptic (tranquilizer) agent.

**DESCRIPTION:** 2 ml and 5 ml ampoules. Each ml contains Droperidol 2.5 mg, and lactic acid for pH adjustment to  $3.4 \pm 0.4$ . 10 ml vials: Each ml contains Droperidol 2.5 mg, with 18 mg methylparaben and 0.2 mg propylparaben, and lactic acid for pH adjustment to  $3.4 \pm 0.4$ .

**INDICATIONS:** INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; • in neurolept analgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

**CONTRAINDICATIONS:** INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

**WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE.** As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should

be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as  $1/4$  to  $1/2$  those usually recommended.

**PRECAUTIONS:** The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy.

Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs. When the EEG is used for postoperative monitoring, it may be



# Documenting a Decade of Significantly Superior Antiemetic Protection

Early Prophylaxis for  
Postoperative  
Nausea  
and Vomiting

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The Premedication That Does More Than Premedicate

### References:

- 1 Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Analg* 1974;53:361-364.
- 2 Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Cur Ther Res* 1984;35:715-720.

found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

**ADVERSE REACTION:** The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and post-operative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic, such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur, if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

**DOSAGE AND ADMINISTRATION:** Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

### Usual Adult Dosage

- I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.
- II. Adjunct to General Anesthesia  
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.  
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

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- III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml., 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

- IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

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When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

**Use in Pregnancy**—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

**ADVERSE REACTIONS**—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

**DOSAGE AND ADMINISTRATION**—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1 to 25 mg/kg. Usually 10 or 20 mg of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

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### REFERENCES:

1. Gyermek L. Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. 1. The effects of glycopyrrolate and pyridostigmine. *Curr Ther Res* 18:377-386, 1975.
2. Ravin MB. Pyridostigmine as an antagonist of d-tubocurarine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg—Curr Res* 54:317-321, 1975.

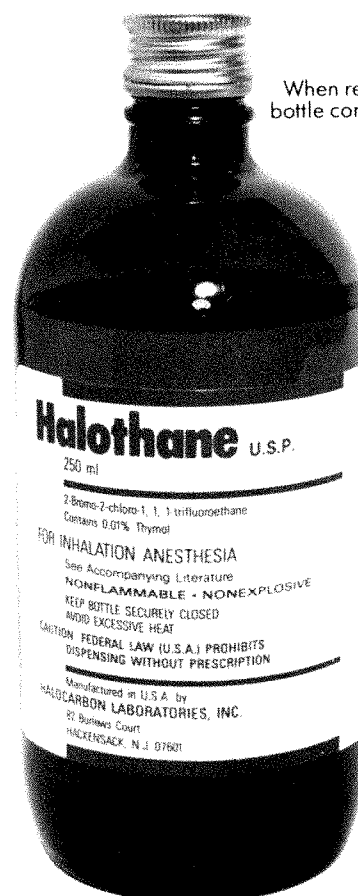


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T. H. Seldon Distinguished Lecture: "*Standards for Excellence*"—M. T. Jenkins, M.D.

### **MEETING SCHEDULE:**

#### **Saturday, March 9:**

Registration—1 to 7 p.m. (Continues throughout meeting)

#### **Sunday, March 10:**

8–5 PM

Review Course Lectures

9–12 PM

Panel—"Cardiac Anesthesia—Case Discussions"

2–5 PM

Panel—"Impact of Legislation and Regulation on Economics in Anesthesiology"

12–5 PM

Scientific and Technical Exhibits Open

6–7 PM

Complimentary Informal Reception

#### **Monday, March 11:**

8–12 PM

Three Concurrent Sessions: Room 1—Review Course Lectures; Rooms 2 and 3—Scientific Papers

1:15–2 PM

**T. H. SELDON DISTINGUISHED LECTURE**

2–5 PM

Three Concurrent Sessions (as above)

9–3 PM

Scientific and Technical Exhibits

#### **Tuesday, March 12:**

8–5 PM

Three Concurrent Sessions (as above)

12–2 PM

Four Concurrent Theme Luncheon Sessions

12–5 PM

NASA Tour

9–1 PM

Scientific and Technical Exhibits (Final Day of Exhibits)

#### **Wednesday, March 13:**

8–5 PM

Three Concurrent Sessions (as above)

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Four Concurrent Theme Luncheon Sessions

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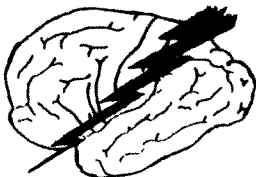
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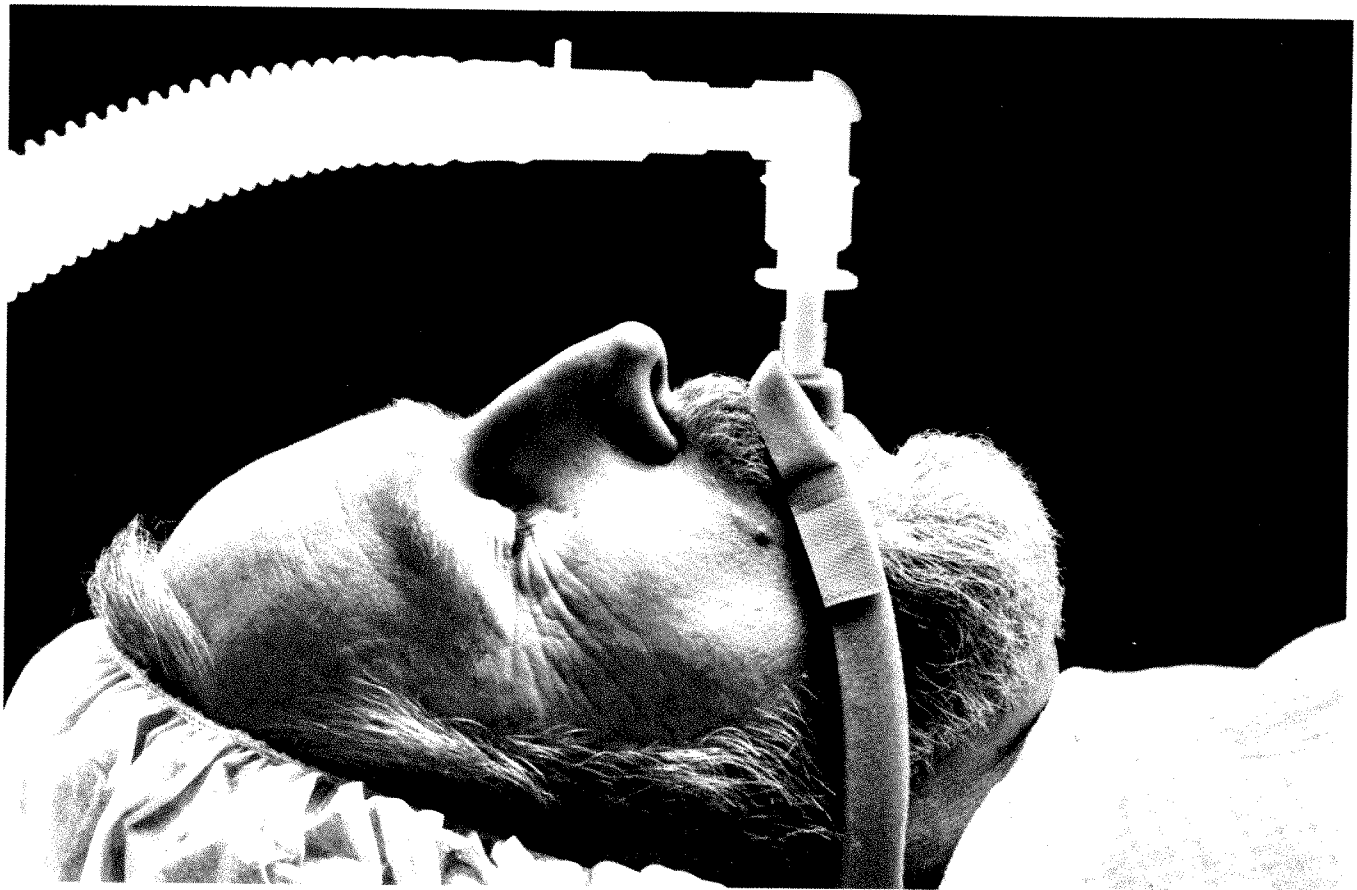
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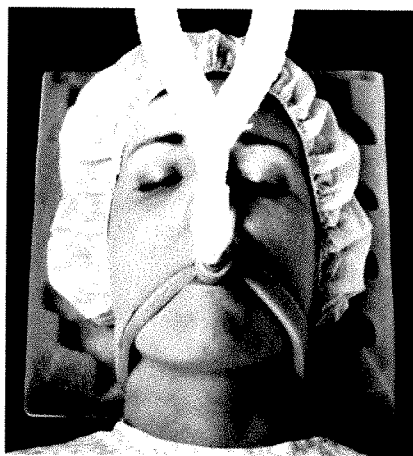
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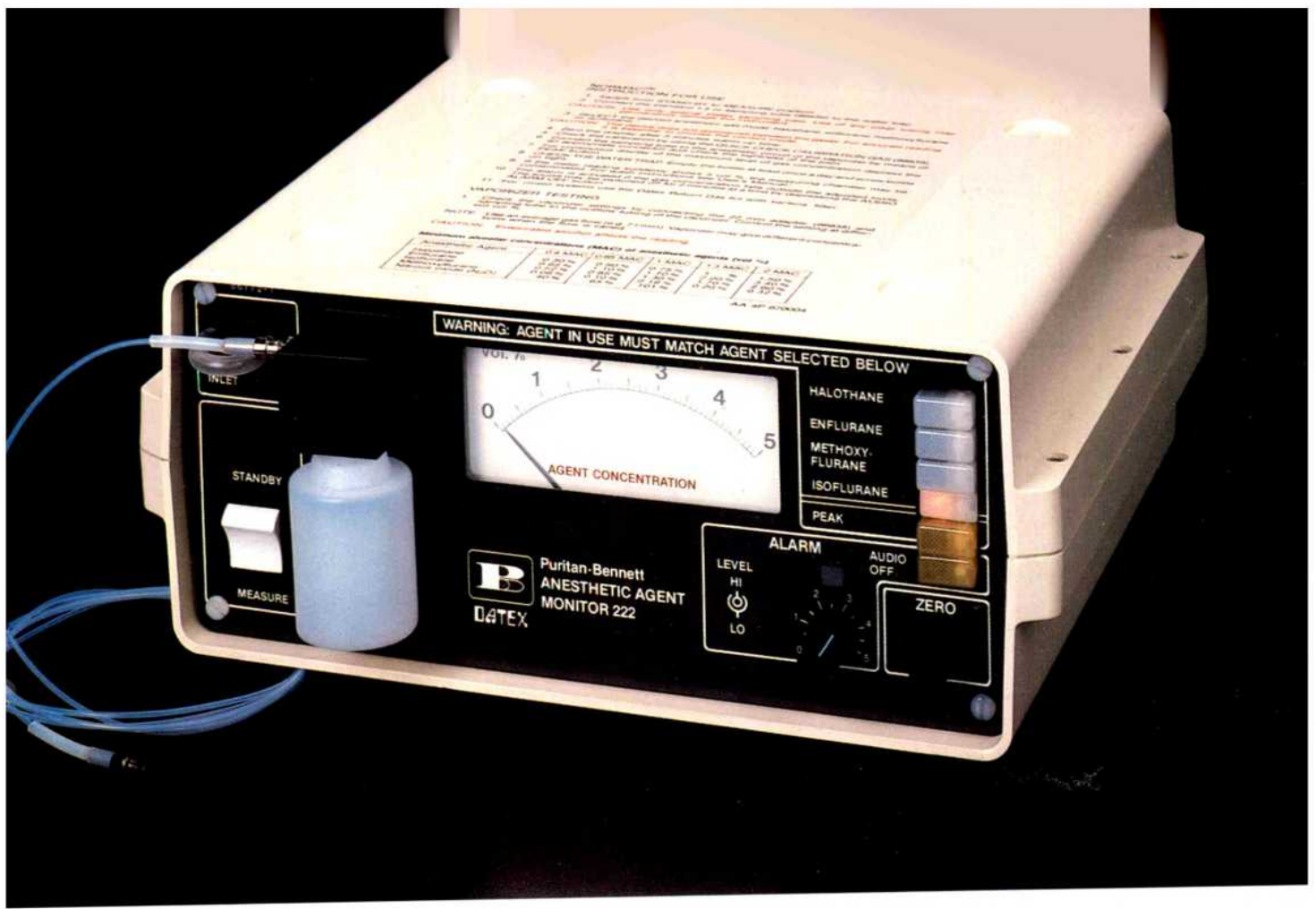
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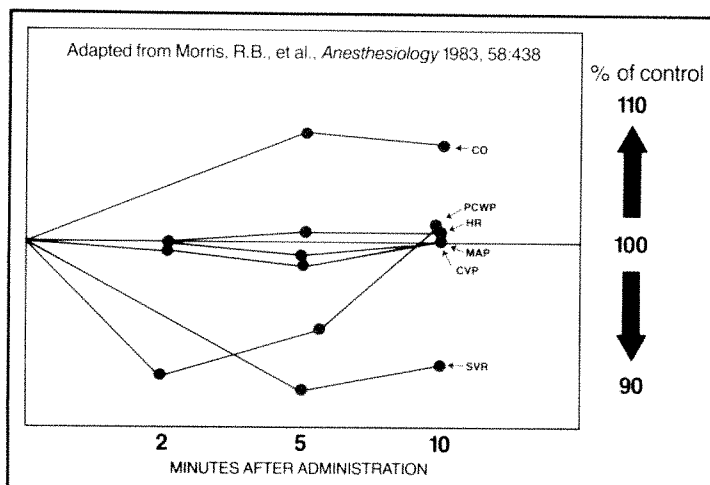
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# In neuromuscular blockade...

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## Free of clinically significant cardiovascular effects

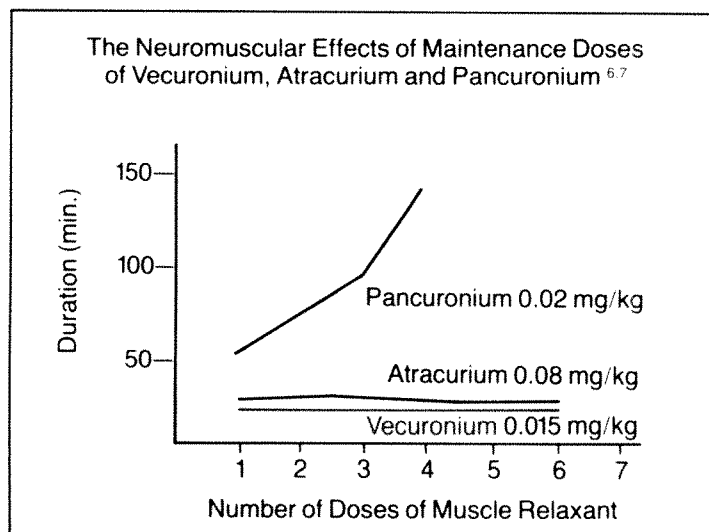
NORCURON is the only surgical muscle relaxant for which no clinically significant adverse cardiovascular effects have been observed in clinical trials.<sup>1,3</sup> This makes NORCURON unique among all neuromuscular blocking agents in clinical use.<sup>4</sup>

The Effect of Non-depolarizing Muscle Relaxants on Histamine Levels, Mean Arterial Pressure and Heart Rate <sup>5</sup>					
Drug	Dose (mg/kg)	xED <sub>95</sub>	Percent of Control		
			Histamine	Mean Arterial Pressure	Heart Rate
tubocurarine	0.5	1	318	78	116
metocurine	0.5	2	212	79	119
atracurium	0.6	3	192	80	108
vecuronium	0.1	1.7	117	100	99
vecuronium	0.2	3.5	87	99	102

## Histamine release unlikely to occur

Histamine release has not been observed with NORCURON...as shown by preliminary clinical experience. In doses up to 3.5 times the ED<sub>95</sub>, it causes no increase in circulating histamine nor does it decrease systemic blood pressure.<sup>5</sup>

Hypotension and tachycardia tend to occur when histamine levels are increased to about 200% of control.<sup>5</sup>



## No clinically significant cumulative effects seen

With NORCURON cumulative effects are not seen in clinical practice. The interval between repeated doses has been found to remain constant between as many as six to ten repeated administrations.<sup>6,7</sup>

# NORCURON<sup>®</sup>

(vecuronium bromide for injection)

## Safety Index and Comparative Safety Ratios<sup>8</sup>

$$\text{Safety Index} = \frac{\text{ED}_{50} \text{ autonomic inhibition}}{\text{ED}_{95} \text{ neuromuscular blockade}}$$

### Comparative Safety Ratios

#### For Vagolytic Effects

gallamine	1:1
pancuronium	3:1
atracurium	25-30:1
vecuronium	60:1

#### For CV/Histamine Related Effects

d-tubocurarine	1:1
metocurine	2:1
atracurium	3:1
vecuronium	*

\*cannot be calculated since it does not cause any CV or histamine related effects

## Outstanding safety profile

The Safety Index helps quantify the improved safety of the newer muscle relaxants on a relative basis. The characteristics of cardiovascular effects and histamine release are areas where the new agents, particularly NORCURON, have made the most significant gains.<sup>8</sup>

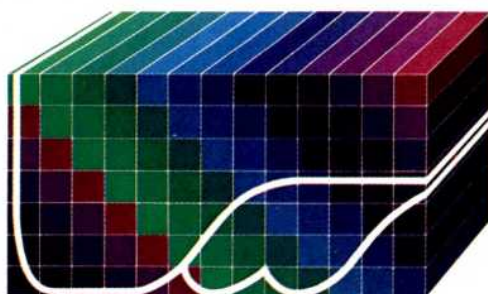
The Safety Index is described as the ED<sub>50</sub> for autonomic inhibition over the ED<sub>95</sub> for neuromuscular blockade.<sup>8</sup>

## A Comparison of Surgical Muscle Relaxants vs. The Ideal<sup>4</sup>

("+" signifies proximity to the ideal)

Characteristic	Vecuronium	Atracurium	Pancuronium	Succinylcholine	D-tubocurarine
Onset of Action	—	—	—	+	—
Histamine Release	+	—	+	+	—
Cardiovascular Side Effects	+	+ / —	—	—	—
Duration of Action	+	+	—	+	—
Cumulative Effects	+	+	—	—	—
Rate of Recovery	+	+	—	+	—
Reversibility	+	+	+	—	+
Potency	+	+	+	—	—
Non-depolarizing	+	+	+	—	+
Metabolite Activity	+	+	+	+	+

\*Currently under evaluation.



## NORCURON<sup>®</sup>

(vecuronium bromide for injection)

### Closest to the ideal

Of the newer short- to intermediate-acting drugs, NORCURON has the most ideal profile, specifically attributable to its outstanding safety features relating to cardiovascular side effects and histamine-releasing properties.<sup>4</sup>





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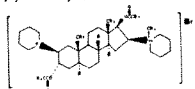
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Norcuron® is supplied as a sterile freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

**CLINICAL PHARMACOLOGY:** Norcuron® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1-3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED<sub>90</sub> (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® (vecuronium bromide for injection) may be decreased by approximately 15% (see Dosage and Administration Section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to a 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started the neuromuscular block produced by Norcuron® (vecuronium bromide for injection) is readily reversed with various anticholinesterase agents, e.g., pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

**Pharmacokinetics:** At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of the injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron® (vecuronium bromide for injection); equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half of the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from the patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary-capillary-wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease.) Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® (vecuronium bromide for injection) has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

**INDICATIONS AND USAGE:** Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** None known.

**WARNINGS:** NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

**PRECAUTIONS:**  
**Renal Failure:** Norcuron® (vecuronium bromide for injection) is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

**Altered Circulation Time:** Conditions associated with slower circulation time in cardiovascular disease, old age, or edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

**Hepatic Disease:** Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in recovery from Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING

**Severe Obesity or Neuromuscular Disease:** Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron® (vecuronium bromide for injection).

**Malignant Hyperthermia:** Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebation. Administration must be accompanied by adequate anesthesia.

**Drug Interactions:** Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY).

The use of Norcuron® (vecuronium bromide for injection) before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied. Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

**Inhalational Anesthetics:** Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

**Antibiotics:** Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce a neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® (vecuronium bromide for injection) during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

**Other:** Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

**Drug/laboratory test interactions:** None known.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

**Pregnancy: Pregnancy Category C:** Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

**Pediatric Use:** Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1 1/2 times as long to recover. Information presently available does not permit recommendations for usage in neonates.

**ADVERSE REACTIONS:** Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

**OVERDOSAGE:** There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Norcuron® (vecuronium bromide for injection) can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve. Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regoni® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

**DOSAGE AND ADMINISTRATION:** Norcuron® (vecuronium bromide for injection) is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain the maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED<sub>90</sub>) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-40 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® (vecuronium bromide for injection) is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

**Dosage in children:** Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1 1/2 times as long to recover. See also sub-section of PRECAUTIONS titled Pediatric use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

**COMPATIBILITY:** Norcuron® is compatible in solution with  
0.9% NaCl solution  
5% glucose in water  
5% glucose in saline  
Lactated Ringers

**HOW SUPPLIED:** 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 12. NDC 0052-0442-10

**STORAGE:** PROTECT FROM LIGHT Store at 15°-30°C (59°-86°F)

**AFTER RECONSTITUTION:** Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION

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# Anesthesia and Analgesia

Journal of the International Anesthesia Research Society

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**DESCRIPTION:** Ativan® (lorazepam) injection, a benzodiazepine with anxiolytic and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

**CLINICAL PHARMACOLOGY:** IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

**INDICATIONS AND USAGE:** In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

**CONTRAINDICATIONS:** Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings.)

**WARNINGS:** PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION, THEREFORE, EQUIPMENT TO MAINTAIN PATIENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

**Pregnancy:** LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chloridiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

**Endoscopic Procedures:** There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

**PRECAUTIONS: General:** Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE AND ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

**Information for Patients:** As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

**Laboratory Tests:** In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

**Drug Interactions:** Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

**Drug/Laboratory Test Interactions:** No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

**Pregnancy:** Pregnancy Category D. See WARNINGS section.

**Labor and Delivery:** There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

**Nursing Mothers:** Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

**Pediatric Use:** There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

**ADVERSE REACTIONS: CNS:** Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE AND ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

**Local Effects:** IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately post-injection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

**Cardiovascular System:** Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

**Respiratory System:** Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

**Other Adverse Experiences:** Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

**DRUG ABUSE AND DEPENDENCE:** As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

**OVERDOSAGE:** Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypoxia, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

**DOSAGE AND ADMINISTRATION:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

**Intramuscular Injection:** For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure. Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

**Intravenous Injection:** For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure. EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

**Administration:** When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP; Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

**HOW SUPPLIED: Ativan®** (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.  
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

For IM or IV injection.

Protect from light. Keep in refrigerator.

**Directions for Dilution for IV Use:** To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

**Wyeth Laboratories**

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# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

## THE B.B. SANKEY IARS ANESTHESIA ADVANCEMENT AWARD

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The B.B. Sankey Anesthesia Advancement Award has been established to expand upon and replace the IARS Research Award. This new award is intended to foster investigative efforts in the fields of anesthesia research, clinical care, education and administration.

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- The official application form for the award must be used. This form, as well as the guidelines for applicants, is available on request to:

Emerson A. Moffitt, MD  
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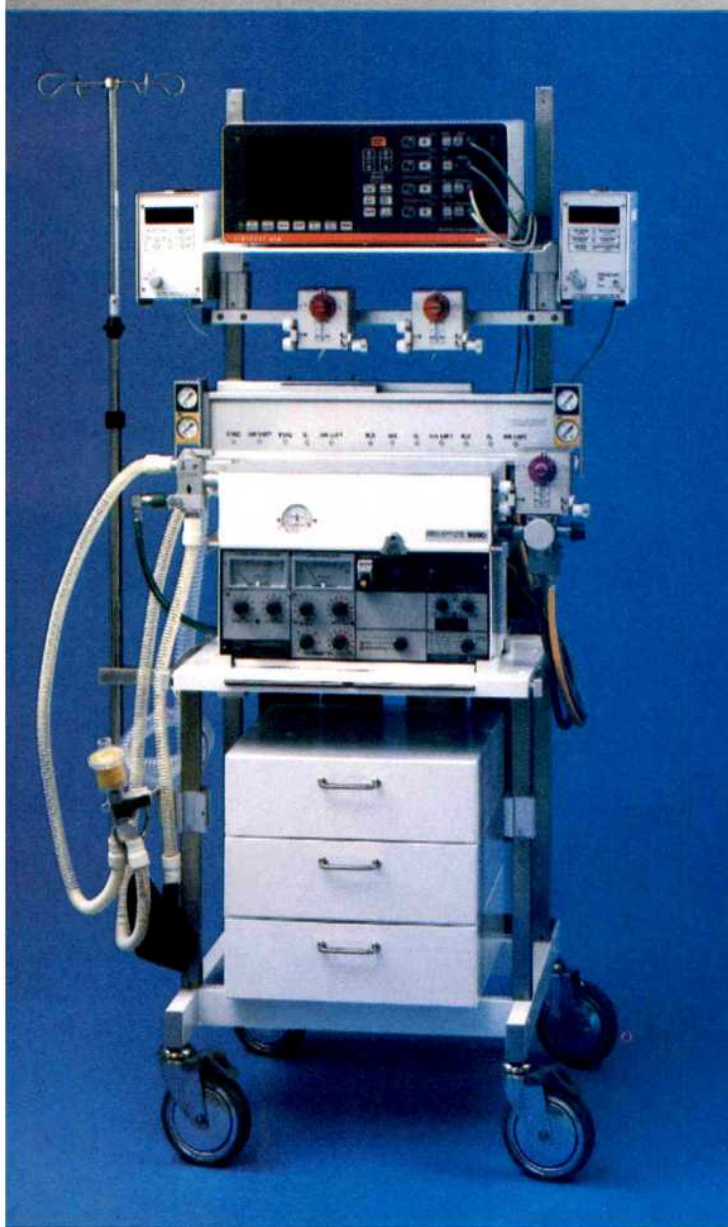
The 1986 Award(s) will be announced at the Annual Meeting (60th Congress) of the International Anesthesia Research Society to be held at Caesars Palace, Las Vegas, Nevada, March 15-19, 1986.



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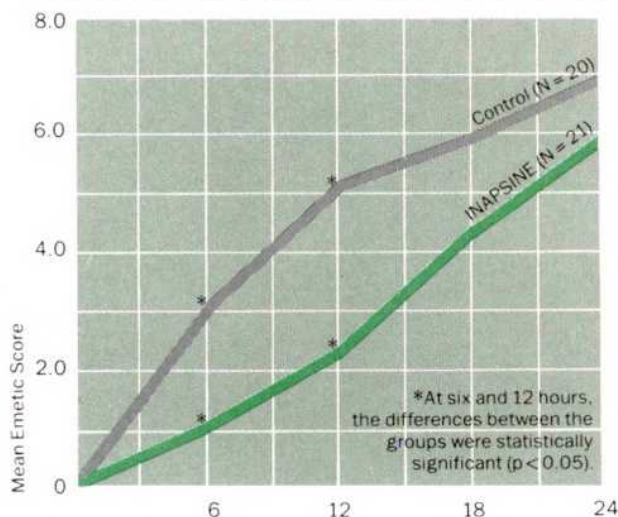


# 1974:

“...we found droperidol [INAPSINE®] to be a safe and effective prophylactic anti-emetic agent in this group of patients at high emetic risk.”<sup>①</sup>

Double-blind study of 41 patients undergoing hysterectomy. Twenty-one patients received 5 mg INAPSINE shortly after surgery began, while 20 patients received placebo. Postoperative emesis was rated according to an emetic scoring system. Patients receiving INAPSINE had significantly less frequent and less severe nausea, retching and vomiting during the first 12 preoperative hours.

INAPSINE vs placebo: mean total emetic scores. The lower the score, the fewer and less severe the incidents of emesis. (Adapted from Patton CM Jr, Moon MR, Dannemiller FJ<sup>①</sup>)



Before prescribing please consult complete prescribing information. The following is a brief summary of the information which follows in the full prescribing information.

**DESCRIPTION:** 2 ml and 5 ml ampoules. Each ml contains droperidol 2.5 mg, and lactic acid for pH adjustment to  $3.4 \pm 0.4$ . Each ml contains Droperidol 2.5 mg, with 18 mg nethylparaben and 0.2 mg propylparaben, and lactic acid for pH adjustment to  $3.4 \pm 0.4$ .

**INDICATIONS:** INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; • in neurolept analgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

**CONTRAINDICATIONS:** INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

**WARNINGS:** FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic, such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should

be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as  $1/4$  to  $1/2$  those usually recommended.

**PRECAUTIONS:** The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

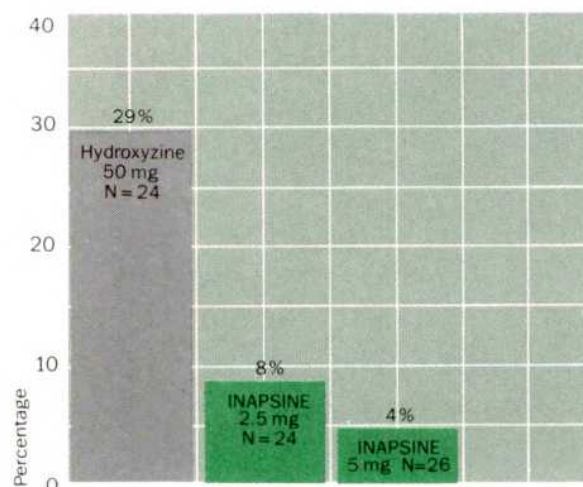
If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy.

# 1984:

“The incidence of postoperative nausea/vomiting...was higher in patients who received hydroxyzine as premedicant compared to those who received droperidol [INAPSINE] ( $p < 0.05$ ).”<sup>②</sup>

Double-blind comparison of INAPSINE 5 mg, INAPSINE 2.5 mg and hydroxyzine 50 mg, combined with meperidine or morphine and glycopyrrolate, as premedication in 74 women undergoing major elective gynecologic surgery. Significantly fewer of the patients receiving INAPSINE experienced postoperative nausea/vomiting than those receiving hydroxyzine ( $p < 0.05$ ).

Percentage of patients experiencing postoperative nausea/vomiting according to premedication ( $p < 0.05$ ). (Based on Mehta P, Theriot E, Mehrotra D, et al<sup>②</sup>)



Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be



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The Premedication That Does More Than Premedicate

### References:

- 1 Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Analg* 1974;53:361-364.
- 2 Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Cur Ther Res* 1984;35:715-720.

found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

**ADVERSE REACTION:** The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and post-operative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur, if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses, however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

**DOSAGE AND ADMINISTRATION:** Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

### Usual Adult Dosage

- I Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.
- II Adjunct to General Anesthesia  
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.  
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

If INNOVAR<sup>®</sup> injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

- III Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

- IV Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

**How Supplied:** 2 ml. and 5 ml. ampoules—packages of 10; 10 ml. multiple-dose vials—packages of 10.

U.S. Patent No. 3161645  
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10  
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# Soothing news for busy anesthesiologists

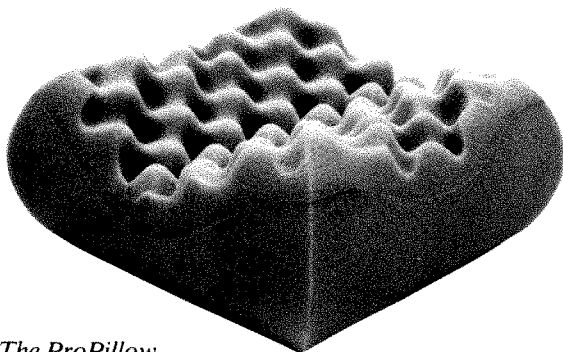
Dr. Smith was having another busy day in surgery. One Swan-Ganz placement had been unusually time-consuming. Plus the patient had been difficult to intubate. To top it off, the pump time had been excessive.

Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

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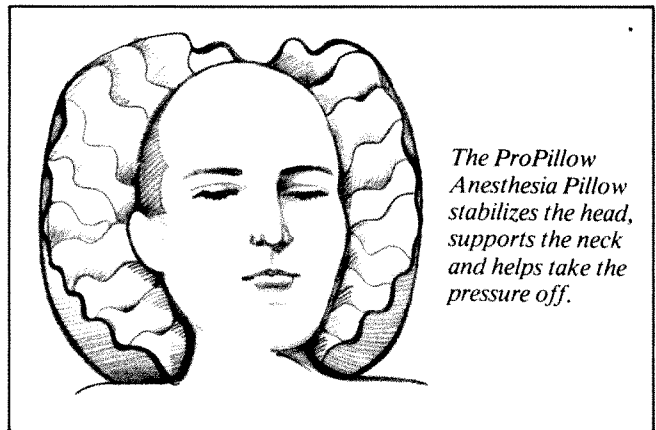
The ProPillow Anesthesia Pillow helps "take off the pressure" to the circulation of the face and scalp during prolonged anesthesia. It's unique "hills and valleys" construction creates a protective effect by evenly distributing the weight of the head and neck. Result: no more pressure in one area greater than any other area. And those precipitous swings in blood pressure are less likely to result in ischemia to the scalp. All this lessens the chance of post-op alopecia.



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PRESERVATIVE-FREE  
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(morphine sulfate injection, USP) CII

# creates new options in pain management

## 1 DURAMORPH® PF provides profound site-selective analgesia.

DURAMORPH® PF delivers preservative-free morphine directly to localized opiate receptors in the spinal cord, selectively blocking nociceptive impulse transmission to the brain's pain centers.

## 2 DURAMORPH® PF prevents postoperative pain when administered at the completion of surgery.

A single 5 mg epidural injection before the onset of postoperative pain provides pain relief associated with many obstetric/gynecologic, orthopedic, thoracic, and abdominal procedures. Use of DURAMORPH® PF is particularly convenient when an epidural catheter is already in place for operative anesthesia.

***“From a humanitarian viewpoint, epidural morphine could be considered the ideal postoperative analgesic . . .”***

#### References:

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### Guidelines for Administration of DURAMORPH® PF

- The epidural route should be used whenever possible; intrathecal administration has been associated with greater potential for immediate or delayed adverse effects.
- Administration should be limited to the lumbar region whenever possible; thoracic injection has been shown to dramatically increase the incidence of respiratory depression.
- Predisposing factors in morphine-related respiratory depression include: thoracic administration,<sup>4</sup> advanced age,<sup>4</sup> reduced ventilatory capacity,<sup>5</sup> high doses,<sup>6</sup> concomitant administration of opioids,<sup>5</sup> supine body position,<sup>7</sup> CNS depressants,<sup>5</sup> and raised intrathoracic pressure.<sup>8</sup> Careful selection of patients, avoidance of opiate premedication, and maintenance of patients in a head-up position may minimize the occurrence of respiratory depression.

**See complete prescribing information**



### **3** DURAMORPH® PF relieves pain for up to 24 hours with a single epidural injection.

DURAMORPH® PF provides extended pain protection with a duration of analgesic effect that is nearly four times longer than that of conventional systemic narcotics (IV morphine).<sup>1</sup>

### **4** DURAMORPH® PF is associated with a low incidence of respiratory depression.

Delayed respiratory depression has been reported; patient monitoring should be continued for at least 24 hours after each dose. Naloxone reverses respiratory depression without diminishing analgesia.

### **5** DURAMORPH® PF maintains patient comfort with virtually no sedation, or loss of motor or sympathetic function.

DURAMORPH® PF out-performs conventional systemic narcotics and local anesthetics in producing site-selective analgesia. Patients are alert and more active participants in their nursing and rehabilitative care.

### **6** DURAMORPH® PF promotes early ambulation and reduces postoperative complications.

Patients receiving DURAMORPH® PF frequently become ambulatory earlier than patients receiving conventional systemic narcotics—often in as little as half the time<sup>1</sup>—which may reduce the risk of postoperative respiratory and thromboembolic complications.<sup>3</sup>

*“Due to absence of sedation and the lack of orthostatic hypotension, high risk patients . . . ambulate early leading to decreased risk for postoperative thromboembolic and respiratory complications.”<sup>2</sup>*

### **7** DURAMORPH® PF may hasten patient recovery and shorten hospital stays.

In a study of patients at high risk of postoperative complications, epidural morphine shortened hospital stays after elective gastropasty from an average of 9 days to 7 days.<sup>3</sup>

### **8** DURAMORPH® PF may mean cost savings in postoperative care.

The benefits of early ambulation, greater patient cooperation with nursing/rehabilitative care, fewer postoperative complications, and shortened hospital stays—offset against the moderately increased costs of short-term postoperative monitoring—may result in a significant net savings in the costs of medical care, an important consideration for institutions dependent on fixed-cost reimbursement policies.

*“... effective analgesia, early ambulation, early normalization of gastrointestinal function, and minimal respiratory complications in the postoperative period all contributed to a shorter hospitalization time in patients receiving epidural morphine analgesia.”<sup>3</sup>*

# PRESERVATIVE-FREE<sup>®</sup> **Duramorph<sup>®</sup> PF** (morphine sulfate injection, USP) CII

## DESCRIPTION

Preservative-free DURAMORPH<sup>®</sup> PF (Morphine Sulfate Injection, USP) is a sterile, pyrogen-free, isobaric solution free of antioxidants, preservatives or other potentially neurotoxic additives, and is intended for intravenous, epidural or intrathecal administration as a narcotic analgesic. Each milliliter contains morphine sulfate 0.5 mg or 1 mg (Warning: May Be Habit Forming) and sodium chloride 9 mg in Water for Injection, pH range is 2.5-6.0. Ampuls are sealed under nitrogen. Each Dosette<sup>®</sup> ampul is intended for SINGLE USE ONLY. Discard any unused portion. DO NOT AUTOCLAVE.

## INDICATIONS AND USAGE

Preservative-free DURAMORPH<sup>®</sup> PF is a systemic narcotic analgesic for administration by the intravenous, epidural or intrathecal routes. It is used for the management of pain not responsive to non-narcotic analgesics. Morphine sulfate, administered epidurally or intrathecally, provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.

## CONTRAINDICATIONS

DURAMORPH<sup>®</sup> PF is contraindicated in those medical conditions which would preclude the administration of opioids by the intravenous route—allergy to morphine or other opiates, acute bronchial asthma, upper airway obstruction.

Administration of morphine by the epidural or intrathecal route is contraindicated in the presence of infection at the injection site, anticoagulant therapy, bleeding diathesis, parenterally administered corticosteroids within a two week period or other concomitant drug therapy or medical condition which would contraindicate the technique of epidural or intrathecal analgesia.

## WARNINGS

DURAMORPH<sup>®</sup> PF administration should be limited to use by those familiar with the management of respiratory depression, and in the case of epidural or intrathecal administration, familiar with the techniques and patient management problems associated with epidural or intrathecal drug administration. Because epidural administration has been associated with lessened potential for immediate or late adverse effects than intrathecal administration, the epidural route should be used whenever possible. Rapid intravenous administration may result in chest wall rigidity.

**FACILITIES WHERE DURAMORPH<sup>®</sup> PF IS ADMINISTERED MUST BE EQUIPPED WITH RESUSCITATIVE EQUIPMENT, OXYGEN, NALOXONE INJECTION, AND OTHER RESUSCITATIVE DRUGS. WHEN THE EPIDURAL OR INTRATHECAL ROUTE OF ADMINISTRATION IS EMPLOYED, PATIENTS MUST BE OBSERVED IN A FULLY EQUIPPED AND STAFFED ENVIRONMENT FOR AT LEAST 24 HOURS.**

**SEVERE RESPIRATORY DEPRESSION UP TO 24 HOURS FOLLOWING EPIDURAL OR INTRATHECAL ADMINISTRATION HAS BEEN REPORTED.**

Morphine sulfate may be habit forming. (See Drug Abuse and Dependence section.)

## PRECAUTIONS

### GENERAL

Preservative-free DURAMORPH<sup>®</sup> PF (Morphine Sulfate Injection, USP) should be administered with extreme caution in aged or debilitated patients, in the presence of increased intracranial/intraocular pressure and in patients with head injury. Pupillary changes (miosis) may obscure the course of intracranial pathology. Care is urged in patients who have a decreased respiratory reserve (e.g., emphysema, severe obesity, kyphoscoliosis).

Seizures may result from high doses. Patients with known seizure disorders should be carefully observed for evidence of morphine-induced seizure activity.

It is recommended that administration of DURAMORPH<sup>®</sup> PF by the epidural or intrathecal routes be limited to the lumbar area. Intrathecal use has been associated with a higher incidence of respiratory depression than epidural use.

Smooth muscle hypertonicity may result in biliary colic, difficulty in urination and possible urinary retention requiring catheterization. Consideration should be given to risks inherent in urethral catheterization, e.g., sepsis, when epidural or intrathecal administration is considered, especially in the perioperative period.

Elimination half-life may be prolonged in patients with reduced metabolic rates and with hepatic or renal dysfunction. Hence, care should be exercised in administering morphine in these conditions, particularly with repeated dosing.

Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be observed carefully for orthostatic hypotension, particularly in transport.

Patients with chronic obstructive pulmonary disease and patients with acute asthmatic attack may develop acute respiratory failure

with administration of morphine. Use in these patients should be reserved for those whose conditions require endotracheal intubation and respiratory support or control of ventilation.

## DRUG INTERACTIONS

Depressant effects of morphine are potentiated by either concomitant administration or in the presence of other CNS depressants such as alcohol, sedatives, antihistaminics or psychotropic drugs (e.g., MAO inhibitors, phenothiazines, butyrophenones and tricyclic antidepressants). Premedication or intra-anesthetic use of neuroleptics with morphine may increase the risk of respiratory depression.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**  
Studies of morphine sulfate in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

## PREGNANCY

**Teratogenic effects—Pregnancy Category C.** Animal reproduction studies have not been conducted with morphine sulfate. It is also not known whether morphine sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Morphine sulfate should be given to a pregnant woman only if clearly needed.

**Nonteratogenic effects.** Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

## LABOR AND DELIVERY

Intravenous morphine readily passes into the fetal circulation and may result in respiratory depression in the neonate. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the neonate. In addition, intravenous morphine may reduce the strength, duration and frequency of uterine contraction resulting in prolonged labor.

Epidurally and intrathecally administered morphine readily passes into the fetal circulation and may result in respiratory depression of the neonate. Controlled clinical studies have shown that epidural administration has little or no effect on the relief of labor pain.

However, studies have suggested that in most cases 0.2 to 1 mg of morphine intrathecally provides adequate pain relief with little effect on the duration of first stage labor. The second stage labor, though, may be prolonged if the parturient is not encouraged to bear down. A continuous intravenous infusion of naloxone, 0.6 mg/hr, for 24 hours after intrathecal injection may be employed to reduce the incidence of potential side effects.

## NURSING MOTHERS

Morphine is excreted in maternal milk. Effect on the nursing infant is not known.

## PEDIATRIC USE

Safety and effectiveness in children have not been established.

## ADVERSE REACTIONS

The most serious side effect is respiratory depression. Because of

delay in maximum CNS effect with intravenously administered drug (30 min), rapid administration may result in overdosing. Bolus administration by the epidural or intrathecal route may result in early respiratory depression due to direct venous redistribution of morphine to the respiratory centers in the brain. Late (up to 24 hours) onset of acute respiratory depression has been reported with administration by the epidural or intrathecal route and is believed to be the result of rostral spread. Reports of respiratory depression following intrathecal administration have been more frequent, but the dosage used in most of these cases has been considerably higher than that recommended. This depression may be severe and could require intervention (See Warnings and Overdose sections). Even without clinical evidence of ventilatory inadequacy, a diminished CO<sub>2</sub> ventilation response may be noted for up to 22 hours following epidural or intrathecal administration.

While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulating catecholamines. Excitation of the central nervous system resulting in convulsions may accompany high doses of morphine given intravenously. Dysphoric reactions may occur and toxic psychoses have been reported.

Epidural or intrathecal administration is accompanied by a high incidence of pruritus which is dose related but not confined to site of administration. Nausea and vomiting are frequently seen in patients following morphine administration. Urinary retention which may persist for 10-20 hours following single epidural or intrathecal administration has been reported in approximately 90% of males. Incidence is somewhat lower in females. Patients may require catheterization (see Precautions). Pruritus, nausea/vomiting and urinary retention frequently can be alleviated by the intravenous administration of low doses of naloxone (0.2 mg).

Tolerance and dependence to chronically administered morphine, by whatever route, is known to occur (see Drug Abuse and Dependence section).

Miscellaneous side effects include constipation, headache, anxiety, depression of cough reflex, interference with thermal regulation and oliguria. Evidence of histamine release such as urticaria, wheals and/or local tissue irritation may occur.

In general, side effects are amenable to reversal by narcotic antagonists. NALOXONE INJECTION AND RESUSCITATIVE EQUIPMENT SHOULD BE IMMEDIATELY AVAILABLE FOR ADMINISTRATION IN CASE OF LIFE-THREATENING OR INTOLERABLE SIDE EFFECTS.

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance:** Morphine sulfate is a Schedule II substance under the Drug Enforcement Administration classification.

**Abuse:** Morphine has recognized abuse potential.

**Dependence:** Cerebral and spinal receptors may develop tolerance dependence independently, as a function of local dosage. Care must be taken to avert withdrawal in those patients who have been maintained on parenteral/oral narcotics when epidural or intrathecal administration is considered. Withdrawal may occur following chronic epidural or intrathecal administration, as well as the development of tolerance to morphine by these routes. (See Nonteratogenic effects under Pregnancy.)

## OVERDOSAGE

Overdosage is characterized by respiratory depression with or without concomitant CNS depression. Since respiratory arrest may result either through direct depression of the respiratory center or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone, is a specific antidote. Naloxone (usually 0.4 mg) should be administered intravenously, simultaneously with respiratory resuscitation. As the duration of effect of naloxone is considerably shorter than that of epidural or intrathecal morphine, repeated administration may be necessary. Patients should be closely observed for evidence of renarcotization. **Note:** Respiratory depression may be delayed in onset up to 24 hours following epidural or intrathecal administration. In painful conditions, reversal of narcotic effect may result in acute onset of pain and release of catecholamines. Careful administration of naloxone may permit reversal of side effects without affecting analgesia. Parenteral administration of narcotics in patients receiving epidural or intrathecal morphine may result in overdosage.

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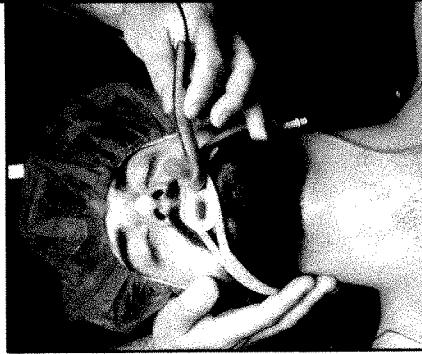
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# The only constant in critical care medicine is change.



In critical care medicine, change is everywhere, and constant. Technologies change. Therapies change. Even economic relationships change, as witnessed by DRGs and their far reaching effects. It is evident that those who practice in the field of critical care, and those who supply the tools they need, must be alert to change, and have the capacity to deal with it.

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#### ACTIONS

ETHRANE® (enflurane) is an inhaled anesthetic. The MAC (minimum alveolar concentration) in middle-aged humans is 1.68% in oxygen and 0.57% in 70% nitrous oxide. The blood/gas partition coefficient is 1.91 at 37°C.

Enflurane obtunds pharyngeal and laryngeal reflexes. Changes in the inspired concentration of enflurane can rapidly change anesthetic depth. Enflurane depresses ventilation, and deeper levels of anesthesia can produce high PaCO<sub>2</sub> levels with spontaneous ventilation.

Blood pressure and cardiac output decrease with induction of anesthesia. Surgical stimulation tends to restore these variables to near normal levels. Increases in depth of anesthesia decrease pressure and output. Heart rate and ventricular rhythm are little affected by enflurane. Enflurane may slightly sensitize the heart to the arrhythmogenic effects of epinephrine.

Enflurane, alone, may produce muscle relaxation adequate for intra-abdominal operations. Nondepolarizing muscle relaxants, especially pancuronium and d-tubocurarine, are potentiated.

Analgesic concentrations of enflurane (0.25% to 1%) do not significantly depress the rate or force of uterine contraction, and normally do not appreciably affect uterine blood loss or Apgar scores. Concentrations of 1% to 2% depress the rate and force of uterine contraction, and 2% to 3% may abolish contractions. Concentrations of 1.5% to 3% diminish or abolish the uterine response to oxytocin. Concentrations exceeding 1% for vaginal delivery or cesarean section may increase uterine bleeding. In patients given

1% enflurane in 70% nitrous oxide for therapeutic termination of pregnancy, mean estimated blood loss is 40 ml—versus 20 ml in patients given only a local anesthetic. The peak levels of serum fluoride after enflurane anesthesia in humans (average 15 µM/l) are well below the 50 µM/l threshold for minimal renal damage in normal patients. However, patients taking isoniazid or other hydrazine-containing compounds may metabolize more enflurane, and peak serum fluoride levels can exceed 50 µM/l.

#### CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE® (enflurane) or other halogenated anesthetics. Known or suspected genetic susceptibility to malignant hyperthermia.

#### WARNINGS

Convulsive activity may be associated with the use of enflurane, particularly with deep anesthesia (greater than 3% enflurane) and/or with hypoxemia.

Only vaporizers producing predictable concentrations of enflurane should be used. Hypotension and respiratory depression can serve as indicators of deeper levels of anesthesia. Greater circulatory depression may result from enflurane administration in patients who are hypovolemic or who have myocardial dysfunction.

If unexplained hepatic dysfunction followed a previous exposure to a halogenated anesthetic, consideration should be given to use of an agent other than enflurane.

#### PRECAUTIONS

**General:** ETHRANE® (enflurane) should be used cautiously in patients with a medical or drug history suggesting a greater susceptibility to cortical stimulation.

**Information for Patients:** As with other anesthetics, enflurane may slightly decrease intellectual function for two to three days after anesthesia. Similarly, small changes in

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## Precise, inhalational control,

to quickly meet patient and operative needs throughout surgery, and to permit a short, dependable recovery period.

## Stability of heart rhythm,

a noteworthy advantage of enflurane anesthesia, particularly when epinephrine for hemostasis is required.

## Reduction in relaxant requirement

and a predictable recovery of neuromuscular function.

mood and symptoms may persist for several days after administration.

**Laboratory Tests:** Bromsulfalein (BSP) retention occasionally is mildly increased post-operatively. This may be the result of surgery itself since anesthesia for 5 to 7 hours in volunteers does not increase BSP. Glucose and white blood count increase intra-operatively. Glucose elevation should be considered in diabetic patients.

**Pregnancy Category B:** Reproduction studies in rats and rabbits given four times the human dose of enflurane revealed no impairment of fertility or harm to the fetus. However, no adequate studies have been done in pregnant women, and enflurane should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Enflurane may be excreted in human milk and caution should be exercised when enflurane is administered to a nursing mother.

**Malignant Hyperthermia:** In susceptible individuals, enflurane may trigger a hypermetabolic state and the clinical syndrome of malignant hyperthermia. The syndrome includes muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure (these nonspecific signs also may appear with light anesthesia, acute hypoxia, etc.). The increase in metabolism may elevate temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and increase the usage of the CO<sub>2</sub> absorption system (hot canister). PaO<sub>2</sub> and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support, and management of electrolyte-fluid-acid-base derangement. Renal failure may appear and urine flow should be sustained if possible.

## ADVERSE REACTIONS

1. Malignant hyperthermia (see PRECAUTIONS). 2. Deep levels of enflurane anesthesia and/or light levels with hypocapnia may produce convulsive activity. 3. Hypotension and respiratory depression may occur. 4. Arrhythmias, shivering, nausea, and vomiting have been reported. 5. Leukocytosis has been observed. 6. Unexplained mild, moderate, and severe liver injury may rarely follow anesthesia with enflurane.

## OVERDOSAGE

To treat overdosage, stop drug administration, establish a clear airway, and assist or control ventilation with pure oxygen.

## DOSAGE AND ADMINISTRATION

Before administration, consult complete information in package insert. The concentration of ETHRANE® (enflurane) being delivered should be known. Only use vaporizers calibrated specifically for enflurane, or vaporizers from which delivered concentrations can easily and readily be calculated.

## HOW SUPPLIED

ETHRANE (enflurane) is packaged in 125 and 250 ml amber-colored bottles.  
125 mL—NDC 10019-350-50  
250 mL—NDC 10019-350-60

**Storage:** Store at room temperature.

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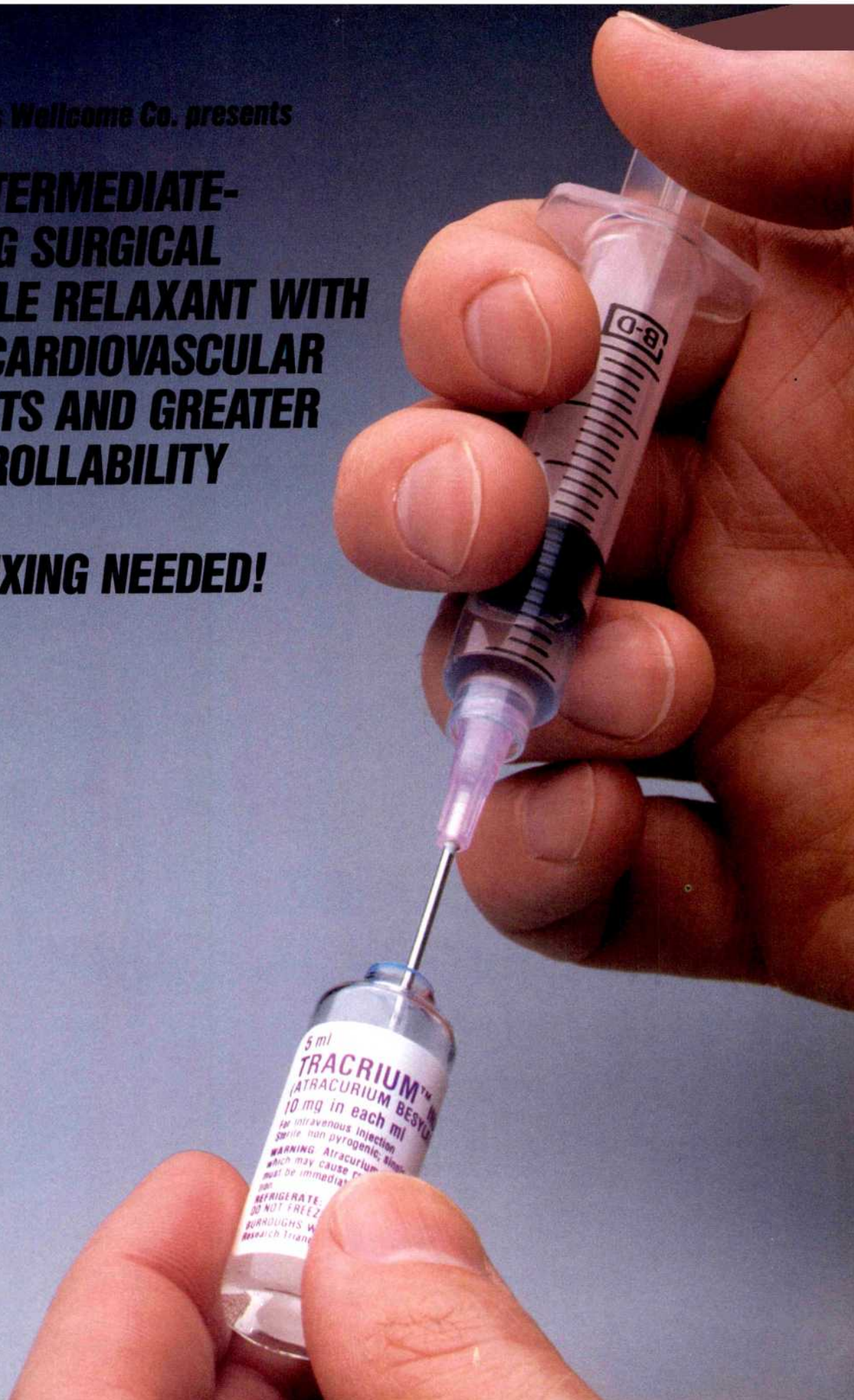
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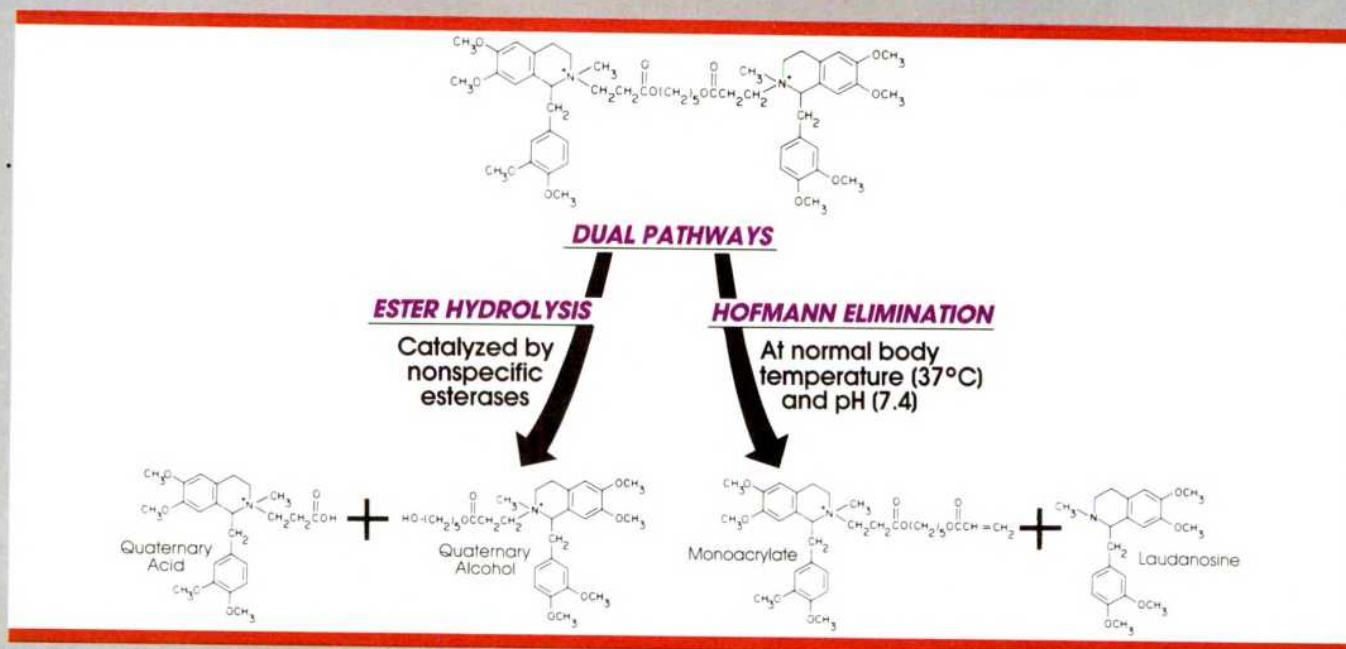
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□ *Tracrium® Injection (atracurium besylate)* is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:

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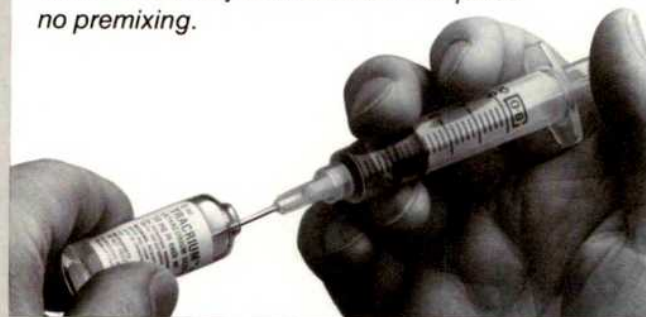
These attributes make *Tracrium* a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."<sup>1</sup>

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."<sup>2</sup>

## Convenient and Ready to Use

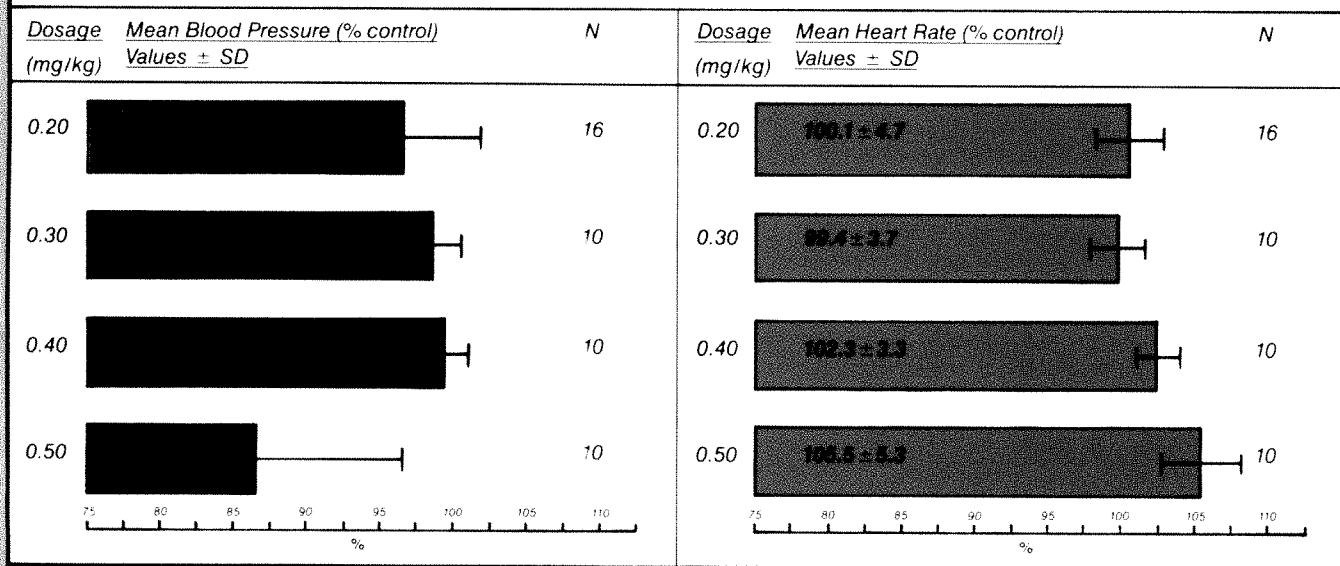
*Tracrium* is easily administered—requires no premixing.



## Few Cardiovascular Effects at Recommended Dosages

□ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.

### Cardiovascular effects of atracurium



Adapted from Basta et al.<sup>3</sup>

## No Cumulative Effects Upon Recovery, After Multiple Doses

- Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time
- Once recovery begins, it is relatively rapid and independent of dose
- This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative...."<sup>1</sup>

## Minimal Histamine Release

- Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine
- Clinically significant histamine release occurs well within the clinical dosage range (at ED<sub>95</sub>) for curare, at the upper limits of the clinical dosage range (at 2 × ED<sub>95</sub>) for metocurine and outside the clinical dosage range (at 3 × ED<sub>95</sub>) for atracurium<sup>4</sup>
- The lack of hemodynamic changes due to Tracrium suggests minimal histamine release

Please see brief summary of prescribing information on the following page.

#### REFERENCES:

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2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. *Anesth Analg* 1982; 61:730-734.
3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. *Anesth Analg* 1982; 61:723-729.
4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. *Anesthesiology* 1982; 57: A261.

**TRACRIUM® INJECTION**  
(atracurium besylate)



# TRACRIUM® INJECTION

## (atracurium besylate)

**DESCRIPTION:** Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

**INDICATIONS AND USAGE:** Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it.

**WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebation. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

### PRECAUTIONS:

**General:** Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** The neuromuscular blocking action of Tracrium may be enhanced by enflurane, isoflurane, halothane, certain antibiotics, especially the aminoglycosides and polymyxins, lithium, magnesium salts, procainamide, or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Pregnancy: Teratogenic Effects:** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of a neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 2 years have not been established.

**ADVERSE REACTIONS:** Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

In the United Kingdom, where Tracrium has been marketed since December, 1982, the most frequent adverse reactions reported in association with the use of Tracrium are cutaneous histamine-like reactions, bronchospasm, and bradycardia. These have been reported to occur in about one in 10,000 patients. Less frequent adverse reactions are hypotension, heart arrest, tachycardia, cyanosis, and apnea, which have been reported to occur in approximately one in 100,000 patients.

**DOSAGE AND ADMINISTRATION:** Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

**HOW SUPPLIED:** Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0840-10).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4178507

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**TRACRIUM® INJECTION**  
(atracurium besylate)

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# TRACRIUM INJECTION

## (atracurium besylate)



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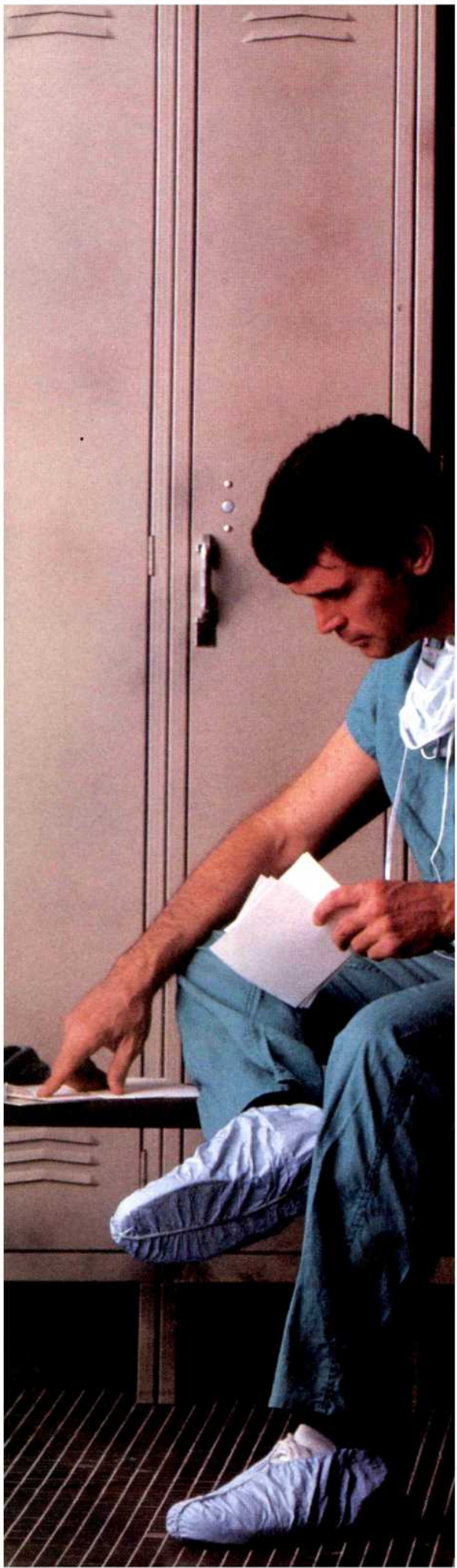
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#### REFERENCES

1. Pierce HE: An effective method of inducing analgesia and anesthesia for dermatoplastic surgery in an office. *J Dermatol Surg Oncol* 1981;7:495-496.
2. Cook TA: Butorphanol tartrate: An intravenous analgesic for outpatient surgery. *Otolaryngol Head Neck Surg* 1983;9:251-254.
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4. Skaredoff MN, Viguera MG: Double-blind comparison of butorphanol and morphine in balanced anesthesia. *Anesthesiology Review* 1980;7 (No. 10):36-39.

**BRISTOL®**

**Stadol® (Butorphanol tartrate)**  
**Brief Summary of Prescribing Information**

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(2)12/10/79

**INDICATIONS AND USAGE**—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of parturient pain.

**CONTRAINDICATIONS**—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

**WARNINGS**—**Patients Physically Dependent on Narcotics:** Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

**Drug Dependence:** Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

**Head Injury and Increased Intracranial Pressure:** Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

**Cardiovascular Effects:** Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

**PRECAUTIONS—Certain Respiratory Conditions:** Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

**Impaired Renal or Hepatic Function:** Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

**Biliary Surgery:** Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

**Usage as a Preoperative or Preanesthetic Medication:** Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

**Usage in Balanced Anesthesia:** The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.

**Usage in Pregnancy:** The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient. Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

**Usage in Labor and Delivery:** Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

**Usage in Nursing Mothers:** The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

**Usage in Children:** Safety and efficacy in children below age 18 years have not been established.

**ADVERSE REACTIONS**—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:

**CNS:** nervousness, unusual dreams, agitation, euphoria, hallucinations

**Autonomic:** flushing and warmth, dry mouth, sensitivity to cold

**Cardiovascular:** palpitation, increase or decrease of blood pressure

**Gastrointestinal:** vomiting

**Respiratory:** slowing of respiration, shallow breathing

**Dermatological:** rash or hives

**Eye:** diplopia or blurred vision

**OVERDOSAGE—Manifestations:** Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

**Treatment:** The immediate treatment of suspected Stadol overdosage is intravenous naloxone.

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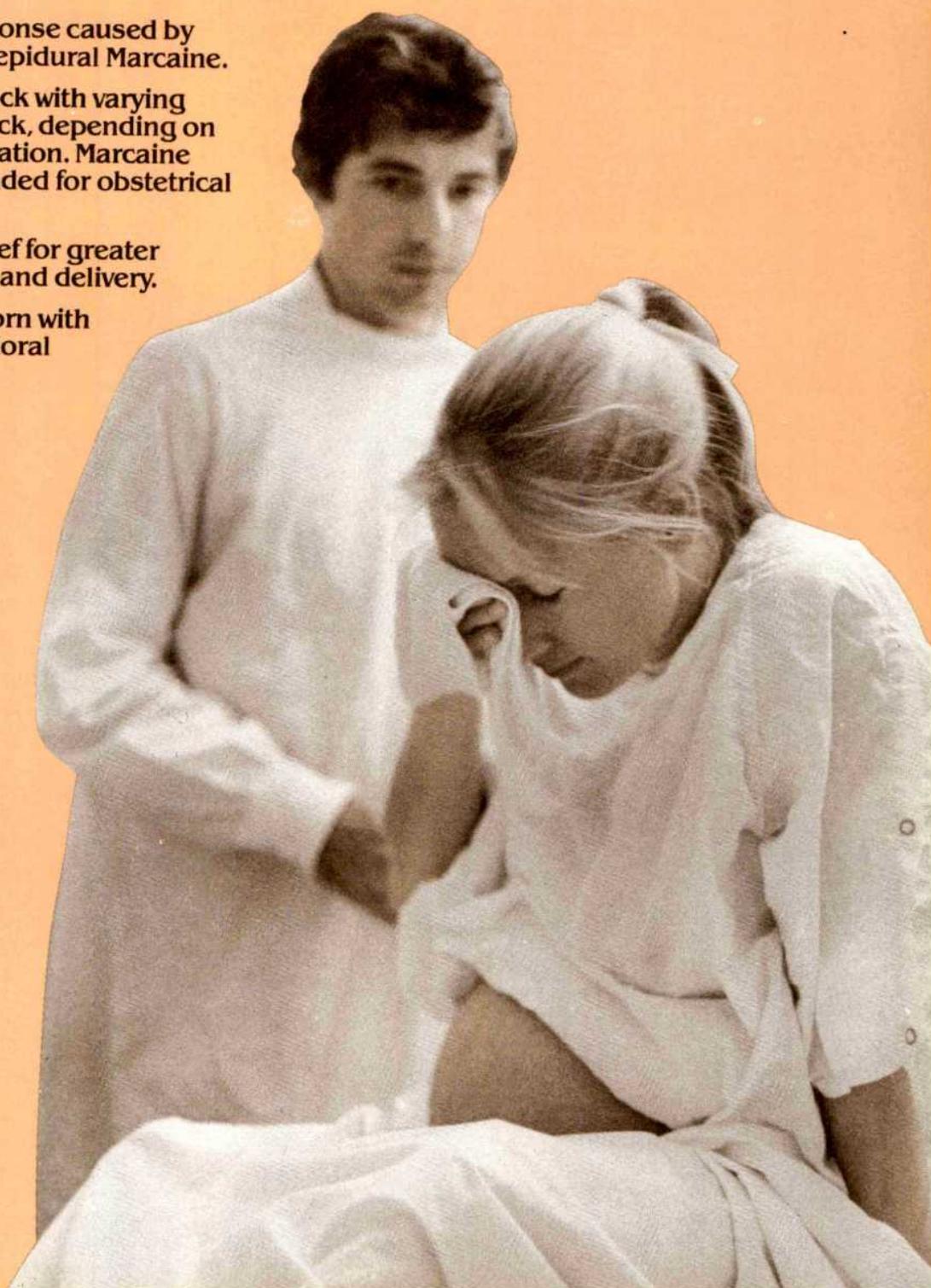
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## WARNINGS

THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY.

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS, PRECAUTIONS AND OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Local anesthetic solutions containing antimicrobial preservatives, ie, those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because their safety has not been established with regard to intrathecal injection—intentionally or not.

It is essential that aspiration for blood or cerebrospinal fluid, where applicable, be done prior to injecting any local anesthetic (the original and all subsequent doses) to avoid intravascular or subarachnoid injection, which can occur even with a negative aspiration.

MARCAINE with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, and used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the tricyclic or imipramine types, severe prolonged hypertension may result.

Pending further experience, MARCAINE administration in children younger than 12 years is not recommended. Mixing, or a prior or concurrent use, of any other local anesthetic with MARCAINE cannot be recommended because such use lacks sufficient clinical data.

There have been reports of cardiac arrest and death with MARCAINE for intravenous regional anesthesia (Bier block). Since information on safe dosages and procedural techniques is lacking, MARCAINE is not recommended.

**PRECAUTIONS: General:** Safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, drugs, and oxygen should be available for immediate use. (See WARNINGS, ADVERSE REACTIONS, OVERDOSAGE.) During major regional nerve blocks, the patient should have IV fluids via an indwelling catheter to assure a functioning intravenous pathway. The lowest effective anesthetic dosage should be used to avoid high plasma levels and serious adverse effects.

**Epidural Anesthesia:** The 0.5% and 0.75% solutions should be administered in increments of 3-5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Administration should be slow, with frequent aspirations before and during the procedure to avoid intravascular injection which is still possible even if aspirations for blood are negative. Syringe aspirations should also be performed before and during each supplemental injection by "continuous" (intermittent) catheter technique. During an epidural procedure, it is recommended that a test dose be administered initially and the effects monitored before giving the full dose. When using continuous catheter technique, test doses should be given prior to both the original and all reinforcing doses because plastic tubing in the epidural space can migrate (etc., as in package insert). Clinical conditions permitting, the test dose should contain epinephrine (10-15 µg has been suggested) to provide warning of unintended intravascular injection. If injected into a blood vessel, this amount is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient who may exhibit only a pulse-rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, heart rate should be monitored for any increase. Patients on beta blockers may not manifest such changes, but blood-pressure monitoring can detect a transient systolic rise. The test dose should also contain 10-15 mg of MARCAINE or an equivalent amount of another local anesthetic to detect unintended intrathecal injection. This will be evidenced within a few minutes by signs of spinal block (eg, decreased gluteal sensation, paresis of the legs or, in the sedated patient, absent knee jerk). Two or 3 mL of MARCAINE 0.5% with epinephrine 1:200,000 contain, respectively, 10 and 15 mg of bupivacaine HCl and 10 and 15 µg of epinephrine. An intravascular or subarachnoid injection is still possible even with negative results of the test dose, which itself may produce an epinephrine-induced cardiovascular or systemic toxic reaction or high spinal effect.

Repeated doses may cause significant increases in plasma levels with each such injection due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the patient's status. Debilitated, elderly, and acutely ill patients should be given reduced doses commensurate with age and physical status. Also use local anesthetics with caution in patients with hypotension or heart failure.

There should be careful and constant monitoring of the patient's cardiovascular and respiratory (adequacy of ventilation) vital signs and state of consciousness after each injection, and kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be warnings of CNS toxicity.

Local anesthetic solutions with a vasoconstrictor should be used cautiously and carefully in body areas supplied by end arteries or with otherwise restricted blood supply (digits, nose, external ear, penis, etc.). Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response, ischemic injury or necrosis may result.

Amide-type anesthetics such as MARCAINE are metabolized by the liver; these drugs (especially repeat doses) should be used cautiously in patients with hepatic disease. Because of an inability to metabolize local anesthetics normally, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations. Also use with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the drug's prolongation of A-V conduction.

Serious dose-related cardiac arrhythmias may occur if preparations containing epinephrine are employed in patients during or following administration of potent inhalation anesthetics. In deciding whether to use these agents concurrently, their combined action on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection should be taken into account (when applicable).

Many drugs used in anesthesia conduct are potentially triggering agents for lamial malignant hyperthermia. Because it is unknown whether amide-type anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard management protocol be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s), and prompt treatment including oxygen, dantrolene IV (see prescribing information before use), and other supportive measures.

**Use in Head and Neck Area:** Small doses of local anesthetics injected into the area, including retrobulbar, dental, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections at larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported and may be due to intraarterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored constantly, with resuscitative equipment and personnel immediately available if needed. Do not exceed dosage recommendations. (See DOSAGE AND ADMINISTRATION.)

**Use in Ophthalmic Surgery:** With MARCAINE 0.75% for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Presence of akinesia alone determines readiness for surgery.

**Use in Dentistry:** Because of the long duration of anesthesia when MARCAINE 0.5% with epinephrine is used dentally, caution patients about inadvertent trauma to tongue, lips, and buccal mucosa. Advise them not to chew solid foods or test the anesthetized area by biting or probing until anesthesia has worn off (up to 7 hours).

**Information for Patients:** When appropriate, inform them in advance of possible temporary loss of sensation and motor activity (usually in the lower body) following administration of caudal or epidural anesthesia, or other possible adverse occurrence noted in package insert.

**Clinically Significant Drug Interactions:** Administering local anesthetic solutions containing epinephrine or norepinephrine to patients receiving MAO inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Thus concurrent use should generally be avoided, in situations when such therapy is necessary, careful monitoring is essential. Concurrent use of vasopressor and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accident. Phenothiazines and butyrophenones may reduce or reverse epinephrine's pressor effect.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term studies in animals of most local anesthetics including bupivacaine have not been conducted. There is no evidence from human data that MARCAINE may be carcinogenic or mutagenic or that it impairs fertility.

**Pregnancy Category C:** Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine was administered to either in doses comparable to 5 to 9 times the maximum recommended daily human dose (400 mg). There are no adequate and well-controlled studies in pregnant women of the drug's effect on fetal development, and potential fetal risk must be justified by potential benefit. This does not exclude use of MARCAINE at term for obstetric anesthesia or analgesia. (See Labor and Delivery.)

**Labor and Delivery:** SEE BOXED WARNING REGARDING OBSTETRIC USE OF 0.75% MARCAINE, and its contraindication in obstetric paracervical block. Local anesthetics cross the placenta rapidly and, when used for epidural, caudal, or pudendal block, can cause varying degrees of maternal, fetal, and neonatal toxicity (See Pharmacokinetics in CLINICAL PHARMACOLOGY). The incidence and degree of toxicity depend upon the procedure performed, and drug type, amount, and technique of administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the CNS, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and left-side positioning will help prevent decrease in blood pressure. Fetal heart rate should be monitored continuously, preferably electronically. Epidural, caudal, or pudendal anesthesia may alter parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong second-stage labor by removing the parturient's reflex urge to bear down, or by interference with motor function. Use of obstetric anesthesia may increase need for forceps assistance.

Some local anesthetic drugs may diminish muscle strength and tone for the first day or two of life. It is unreported with bupivacaine.

Of extreme importance: Avoid aortocaval compression of the gravid uterus during administration of regional block. To do this, maintain the parturient in the left lateral decubitus position, or place a blanket roll or sandbag beneath the right hip to displace the gravid uterus away from the great vessels.

**Nursing Mothers:** It is not known whether local anesthetics are excreted in human milk, because many drugs are, administer with caution.

**Pediatric Use:** Without further experience in children under 12, MARCAINE is not recommended for this group.

**ADVERSE REACTIONS:** A major cause of adverse reactions to amide-type local anesthetics is excessive plasma levels, possibly due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

**Systemic:** The most common acute experiences, demanding immediate countermeasures, involve the CNS and cardiovascular systems. Adverse events are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or unintentional intravascular injection of the solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection during performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea. Also, hypotension due to loss of sympathetic tone, and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia, may occur, leading to secondary cardiac arrest if untreated. Factors influencing plasma protein binding such as acidosis, systemic diseases which alter protein production or competition of other drugs for protein binding sites, may diminish individual tolerance.

**Central Nervous System:** Excitation and/or depression, restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly convulsions. Excitement may be transient, depression being the first manifestation of an adverse reaction. Drowsiness merging into unconsciousness and respiratory arrest may quickly follow. Other CNS effects may be nausea, vomiting, chills, pupillary constriction. Incidence of convulsions varies with the procedure used and total dose administered. In studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of procedures.

**Cardiovascular:** High doses of unintentional intravascular injection may lead to high plasma levels and related myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. (See WARNINGS, PRECAUTIONS, OVERDOSAGE.)

**Allergic:** Rare, and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients administered intrathecally and physiologic and physical effects of dural puncture. High spinal levels of epinephrine-containing solutions. Possible reactions: urticaria, pruritus, erythema, angioneurotic edema (including laryngeal), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, perhaps anaphylactoid symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type anesthetic group reported; value of sensitivity screening is unestablished.

**Neurologic:** Incidence of adverse reactions associated with use of such drugs may be related to the total dose administered, and dependent upon the particular drug use, route of administration, and the patient's physical status. Many effects may be related to technique, with or without the drug being contributory.

In performing caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and physiologic and physical effects of dural puncture. High spinal levels are characterized by leg paralysis, loss of consciousness, respiratory paralysis and bradycardia. Effects following epidural or caudal anesthesia may include: spinal block of varying magnitude (including high or total spinal block), hypotension secondary to spinal block, urinary retention, fecal and urinary incontinence, loss of perineal sensation and sexual function, persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities, and loss of sphincter control—all of which may show slow, incomplete, or no recovery, headache, backache, septic meningitis, meningism, slowing of labor, increased incidence of forceps delivery, cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

**OVERDOSAGE:** Acute emergency during therapeutic local anesthesia is generally related to high plasma levels of unintended subarachnoid injection of the solution. (See ADVERSE REACTIONS, WARNINGS, PRECAUTIONS.)

The first consideration in management is prevention, best accomplished by careful, constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each injection. At the first sign of change, administer oxygen. This measure may prevent convulsions if they have not already occurred. In systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, give immediate attention to establishing and maintaining a patent airway and controlled ventilation with 100% oxygen (the delivery system must permit instant positive airway pressure by mask). Endotracheal intubation may be indicated to meet the need for prolonged ventilatory support or if difficulty is encountered in the maintenance of a patent airway.

If necessary, use drugs to control convulsions. A 50-100 mg bolus IV injection of succinylcholine will paralyze the patient (without CNS or cardiovascular depression) and facilitate ventilation. A 5-10 mg IV bolus of diazepam, or 50-100 mg of thiopental, will permit ventilation and counteract CNS stimulation, but these drugs also depress CNS, respiratory and cardiac function, add to postictal depression, and may cause apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should be administered only by those familiar with use. Immediately after institution of ventilatory measures, circulatory adequacy should be evaluated; supportive treatment may require administration of IV fluids and, when appropriate, a vasopressor (dictated by the clinical situation (eg, ephedrine or epinephrine to enhance myocardial contractile force)).

Recent clinical data from patients experiencing convulsions induced by local anesthetics demonstrated rapid development of hypoxia, hypercarbia, and acidosis, with bupivacaine, within a minute of onset. These observations suggest that O<sub>2</sub> consumption and CO<sub>2</sub> production are greatly increased during the convulsions and emphasize the importance of immediate ventilation with oxygen, if not treated effectively, convulsions and their complications plus myocardial depression from direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities including apnea may occur, underventilation or apnea due to unintentional subarachnoid injection of the solution may also lead to these signs and cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, prolonged resuscitative effort may determine a successful outcome.

In treating systemic toxicity, maternal hypotension, or fetal bradycardia following regional block, avoid aortocaval compression by the gravid uterus. The supine position is dangerous, etc. (as in insert). (See Labor and Delivery in PRECAUTIONS.)

**Composition of Marcaine Solutions:** 0.25%—each mL contains 2.5 mg bupivacaine, 0.5%—each mL contains 5 mg bupivacaine, 0.75%—each mL contains 7.5 mg bupivacaine. All concentrations contain NaCl for isotonicity in Water for Injection.

In multiple-dose vials, each mL also contains 1 mg methylparaben. With epinephrine, each mL also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 mL monothioglycerol, 2 mg ascorbic acid, 0.0017 mL 60% sodium lactate, and 0.1 mg edetate calcium disodium.

1. Ostheimer GW: Neurobehavioral effects of local anesthesia and fetal resuscitation. *Reg Anesth* 1981;6:136-145.
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## Editorial

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### The B. B. Sankey Anesthesia Advancement Award

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The International Anesthesia Research Society was founded in 1922 as a non-profit, non-political scientific and educational organization. The goal, stated by the founders, was "to foster progress and research in all phases of anesthesia." The Society has pursued this goal by publishing *Anesthesia and Analgesia*, the oldest publication in the specialty (1), by conducting an annual Congress, and, more recently, by donating research funds to the American Society of Anesthesiologists and to the Canadian Anaesthetists Society. In 1983, the Board of Trustees established the IARS Research Award, which, in three years, has granted more than \$100,000 in support of five research protocols.

During the 63 years since the IARS was established, enormous change has occurred in almost every aspect of our existence. In North America, the health sciences have become a major, if not overwhelming, aspect of our lives, with the costs of health care equaling about 10% of our gross national product. The practice of medicine is increasingly perceived by the public as a business. Anesthesiology has evolved into a major medical specialty that has made possible the surgical management of a multitude of previously unmanageable conditions. While not all of this progress has been due to the application of the results of clinical or laboratory investigation, the scientific advances in the specialty have been spectacular, and largely financed by government and industry. There have been remarkable innovations in technology, resident education, resource management, and role identification in anesthesiology. A substantial number of our colleagues have become industry consultants, medical school deans, provosts, executive administrators, legislators, and legal practitioners. It appears that anesthesiologists will continue their involvement in these areas while government support for continued progress and discovery is being seriously reduced.

In seeking a suitable means of honoring Dr. B. B. Sankey for his "wise, perceptive, circumspect and imaginative leadership" (quote from the text of the citation presented to Dr. Sankey on the occasion of

his retirement) as IARS Board Executive Secretary for 18 years, the Board of Trustees returned to the original statement of purpose for guidance. The words "all phases of anesthesia" seemed more of a rubric than a codicil in light of current developments, and the decision to expand the concept of the IARS Research Awards was made.

The B. B. Sankey Anesthesia Advancement Awards will be granted to applicants with projects in the areas of clinical care, education, and administration, as well as laboratory and clinical research. By this means, the Board hopes to stimulate creativity in our expanded efforts as a specialty, not only in the laboratory and operating room, but also in the classroom, the clinic, the office, the intensive care unit, and in other areas, as human ingenuity would dictate. If progress is achieved through trial and error, this is a modest encouragement to undertake the trial in many additional areas of the practice of anesthesiology, despite the risk of error.

There undoubtedly will be questions generated by the unique concept of this award. The rules and guidelines, obtainable from the Cleveland office (3645 Warrensville Center Road, Cleveland, OH 44122), are deliberately short and simple. There is no attempt to define or limit the fields identified as research, clinical care, education, and administration, other than that the project must have relevance to the specialty of anesthesiology. Any application that can pass this basic test will be considered. By this means, the Board of Trustees hopes to encourage the same scientific approach that has served so well in the laboratory to guide us toward the identification and solution of problems related to the major changes underway in the overall provision of health-care services.

Edward P. Didier, MD  
Chairman, Board of Trustees  
International Anesthesia Research Society

#### Reference

1. Seldon TH. Anesthesia & analgesia—50 years of publication. *Anesth Analg* 1971;50:571-7.

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## The Effects of Naloxone Associated with the Intrathecal Use of Morphine in Labor

Patricia A. Dailey, MD, G. Lee Brookshire, MD, Sol M. Shnider, MD,  
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DAILEY PA, BROOKSHIRE GL, SHNIDER SM, ABBOUD TK, KOTELKO DM, NOUEIHID R, THIGPEN JW, KHOO SS, RAYA JA, FOUTZ SE, BRIZGYS RV, GOEBELSMANN U, LO MW. The effects of naloxone associated with the intrathecal use of morphine in labor. *Anesth Analg* 1985;64:658-66.

*The efficacy of naloxone in reducing the incidence of side effects after intrathecal injection of morphine and the effects of maternal naloxone administration on the condition of the newborn were evaluated in 40 patients. Patients in labor were given a 1-mg intrathecal injection of morphine and, 1 hr later, either a 0.4-mg bolus of naloxone, followed by a 0.4-0.6 mg/hr intravenous infusion of naloxone, or an intravenous bolus of saline, followed by an intravenous infusion of saline. Intrathecal morphine provided at least 50% pain relief in 78% of patients given naloxone, and in 82%*

*given saline. Intravenous naloxone significantly decreased the incidence of pruritus during labor and delivery. There was no significant decrease in the incidence of nausea, vomiting, somnolence, dizziness, or urinary retention in patients given naloxone. Despite placental transfer of naloxone, neonatal outcome was not adversely affected. For both groups, maternal  $\beta$ -endorphin levels decreased significantly with the onset of analgesia and returned to control levels at delivery. We conclude that intravenous infusion of naloxone reduced pruritus after intrathecal injection of 1 mg of morphine for labor pain without lessening analgesia or adversely affecting maternal or neonatal status.*

**Key Words:** ANALGESICS—morphine. ANESTHESIA—obstetrics. ANESTHETIC TECHNIQUES—spinal. ANTAGONISTS, NARCOTICS—naloxone.

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Morphine administered intrathecally provides substantial, prolonged pain relief during the first and second stages of labor (1-3). Although intrathecal morphine does not produce sympathetic and motor blockade, as do local anesthetics used for regional blocks, intrathecal administration of morphine incurs a high incidence of pruritus, nausea and vomiting, somnolence, and urinary retention (1-5). In addition,

several case reports have described life-threatening respiratory depression after intrathecal morphine (4,6-10). Small doses of parenterally administered naloxone have antagonized the side effects of intrathecally or epidurally administered opiates (1-3); in some instances, analgesia was maintained by naloxone, and in others, it was reduced. We now investigate whether the incidence of side effects could be decreased without also decreasing analgesia. After intrathecal injection of morphine, we compared the effects of intravenous bolus and infusion of either saline or naloxone on the following: the incidence and severity of maternal side effects during labor and delivery, the degree of analgesia obtained, the placental transfer of naloxone, fetal outcome, and  $\beta$ -endorphin plasma levels in the mother and newborn.

### Methods

We studied 40 unpremedicated healthy parturients in their thirty-eighth to forty-second week of gestation

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who were in active or augmented labor, had cervical dilatation of 3–8 cm, and had fetuses in vertex presentation. Patients demonstrating evidence of fetal distress were not studied. We obtained approval from the Committee on Human Research and informed consent from the parturients.

For relief of labor pain, patients were given an intrathecal injection of 1 mg of preservative-free morphine in normal saline (prepared by the A. H. Robins Company). While the patient was lying in the lateral decubitus position, morphine was injected intrathecally at the level of the L2–3 or L3–4 interspace with a 25-gauge spinal needle. Patients were then positioned on their sides and their heads elevated 30°. One hour later, patients were given (determined randomly) either an intravenous bolus of 0.4-mg naloxone followed by an intravenous infusion of naloxone (0.4 mg/hr) in normal saline, or an intravenous bolus of normal saline followed by an intravenous infusion of normal saline. The total volume of both boluses was 40 ml; the initial rate of infusion was 40 ml/hr. The infusion was maintained for 23 hr. Prior to delivery, if side effects (pruritus, nausea, vomiting, somnolence, dizziness, and urinary retention) occurred or became increasingly severe for patients given naloxone, the rate of infusion was increased and/or a bolus of 0.1–0.4 mg naloxone was administered. If no improvement in side effects occurred, promethazine (to treat nausea and vomiting) or diphenhydramine (to treat pruritus) was administered parenterally. If saline alone was being infused, the patient was given promethazine and/or diphenhydramine parenterally. After delivery, for both groups, side effects were initially treated with naloxone. If nausea and vomiting did not resolve with naloxone, patients received promethazine. Diphenhydramine was administered to treat pruritus unresponsive to naloxone.

Uterine activity, fetal heart rate, and fetal heart rate variability were monitored continuously. Periodic assessment of the pain intensity of uterine contractions during labor were made just before the injection of morphine, and then after morphine injection every 15 min for 1 hr, followed by every 30 min until delivery. Using a visual linear analog scale (11), the patient evaluated the intensity of pain. An observer who did not know which fluid was being infused also assessed the patient's pain and its relief, using the following system: 4—no evidence of pain (excellent pain relief); 3—slight pain, as evidenced by a slight grimace at the peak of contractions (good relief; pain more than 50% relieved); 2—moderate pain with contractions, but less than before injection (fair relief; pain less than 50% relieved); 1—pain unchanged (no detectable pain relief); and 0—pain worse than before

injection. If analgesia from the intrathecal injection of morphine was inadequate during labor, patients received epidural analgesia and assessments of pain intensity were discontinued. If additional analgesia was required at delivery, the patients received local infiltration, pudendal block, or epidural anesthesia. Pain intensity was not evaluated at delivery.

At the same times pain intensity was assessed, maternal heart rate, blood pressure, respiratory rate, and the incidence and severity of side effects were recorded by an investigator who knew which fluid was being administered. In addition, after delivery, hourly observations of maternal vital signs and side effects were made until 24 hr after morphine injection. For analysis of PCO<sub>2</sub>, samples of maternal venous blood were obtained before injection; at delivery; and 4, 8, 12, and 24 hr after injection of morphine. Respiratory depression was defined as a respiratory rate of 10 breaths/min or fewer, and/or a venous PCO<sub>2</sub> value > 45 mm Hg. Pruritus was graded according to location and severity; none—patient denies pruritus, even if observed rubbing skin; mild—patient aware of localized pruritus but not uncomfortable; moderate—patient aware of generalized pruritus but not uncomfortable; and severe—patient has localized or generalized pruritus and is uncomfortable. Nausea was assessed as being mild, moderate, or severe. Vomiting was evaluated according to frequency: mild—one occurrence of emesis; moderate—two to four occurrences; and severe—more than four occurrences. Somnolence or dizziness was graded as mild, moderate, or severe. Urinary retention was defined as an inability to void that necessitated catheterization. Patients who underwent catheterization of the urinary bladder prior to delivery by forceps or vacuum extraction were also considered to have urinary retention.

In evaluating the progress of labor, we used the following classifications of abnormal progress: slow-slope active phase—cervical dilatation of less than 0.7 cm/hr in nulliparas and 1.1 cm/hr in multiparas; active-phase arrest—no change in cervical dilatation for 2 hr; and prolonged second stage—a second stage of labor lasting longer than 2 hr.

We evaluated the condition of the infant using the following data: Apgar scores at 1 and 5 min, the time-to-sustained respiration (TSR), blood-gas values for venous and arterial blood obtained from a doubly clamped segment of umbilical cord, and the Neurologic and Adaptive Capacity Scores (NACS) (12) at 15 min, 2 hr, and 24 hr after birth. An infant having an Apgar score of 7 or higher and a NACS of 35 or higher was considered vigorous. The investigator evaluating the infant did not know which infusion was being given to the mother.

To measure plasma  $\beta$ -endorphin concentrations, we obtained venous blood samples from an indwelling maternal catheter (just before injection of morphine, 1 and 2 hr after injection, and at delivery), and from a doubly clamped segment of umbilical cord (at delivery). Concentrations were measured using radioimmunoassay after silicic acid extraction assay and gel chromatography (13). The assay is sensitive to 7 fmol/ml (one femtomole of  $\beta$ -endorphin is equal to 3.465 pg) if a 5-ml aliquot is analyzed. Intraassay and interassay coefficients of variation are 6.8% and 11%, respectively.

At delivery, venous blood samples were also obtained from the umbilical cord segment for naloxone measurements. Serum naloxone concentration was determined using a reversed-phase, high-performance liquid chromatographic method and electrochemical detection (DuPont Pharmaceuticals, Stine Laboratory, Newark, DE). The assay is sensitive to 0.2 ng/ml. The intraassay variation at 1 ng/ml ( $n = 3$ ) was 10.2%.

For the purpose of comparison, each patient's assessment of pain was standardized to her initial evaluation of pain using the data from the visual linear analog scale and the equation shown in Figure 1. Data are presented as mean values and standard errors of the mean. Data were analyzed using the Mann Whitney U-test, Student's unpaired and paired  $t$ -test, and Fisher's exact test. A  $P$  value of less than 0.05 was considered statistically significant.

## Results

### *Progress of Labor and Delivery*

The 17 patients given intravenous saline and the 23 given intravenous naloxone were comparable in age, height, weight, weeks of gestation, parity, cervical dilatation at the time of morphine injection, incidence of oxytocin augmentation of labor, fetal position at delivery, and duration of analgesia before delivery (time from administration of intrathecal morphine to delivery) (Table 1). Fifty-five percent of patients were primiparous; 45% of patients had augmentation of labor with oxytocin. The mean cervical dilatation at the time of morphine injection was  $4.6 \pm 0.22$  cm. The mean interval between injection of morphine and delivery was  $382 \pm 57$  min for patients given saline, and  $269 \pm 29$  min for patients given naloxone ( $P > 0.05$ ).

The progress of the active phase of labor was normal in 82% of patients given saline and in 91% of patients given naloxone (Table 2). The second stage of labor was prolonged in 29% of patients given saline and in 26% of patients given naloxone.

$$\left[ \frac{\begin{array}{l} \text{ANALOG LINE REPRESENTING} \\ \text{PAIN BEFORE MORPHINE (mm)} \end{array} - \begin{array}{l} \text{ANALOG LINE REPRESENTING} \\ \text{PAIN AFTER MORPHINE (mm)} \end{array}}{\begin{array}{l} \text{ANALOG LINE REPRESENTING} \\ \text{PAIN BEFORE MORPHINE (mm)} \end{array}} \right] \times 100 = \text{PERCENTAGE OF MATERNAL PAIN RELIEF}$$

Figure 1. Equation used to calculate the parturient's assessment of relief of labor pain (as a percentage) after intrathecal injection of morphine. Data from the "visual linear analog scale" were used. Maternal pain relief was the percentage of change from her initial assessment of pain, i.e., before morphine was administered.

All patients in the saline group and all but one patient in the naloxone group delivered vaginally. No significant differences existed between groups in the method of delivery or in the anesthesia used for delivery, with one exception: the incidence of midforceps delivery was significantly lower for patients given naloxone (Table 2). Eighty percent of patients had spontaneous vaginal delivery; 41% of these patients required no additional anesthesia for delivery. The patient who had a cesarean delivery was given general anesthesia; the indication for cesarean delivery was cephalopelvic disproportion and a prolonged second stage of labor. The baby weighed 4460 g at birth.

### *Obstetric Analgesia*

Based on data from the visual linear analog scale, 82% of patients given saline and 78% of those given naloxone obtained at least 50% pain relief ( $P > 0.05$ ). Although analgesia, as assessed by the parturient, tended to be less in the naloxone group than in the saline group, this was not statistically significant (Fig. 2). One hour after intrathecal morphine, 63% of patients given saline and 52% given naloxone had good-to-excellent analgesia (i.e., a pain score of 3 or 4), as assessed by the investigator (Fig. 3). Five hours after intrathecal morphine, 78% and 86% of patients in the saline and naloxone groups, respectively, who had not yet delivered had good-to-excellent analgesia for labor. Based on the investigator's assessment, 53% and 57% of patients given saline and naloxone, respectively, achieved complete pain relief for variable periods of time during labor. One patient in each group required epidural analgesia during the first stage of labor.

Mean maternal  $\beta$ -endorphin levels decreased significantly with the onset of analgesia. Before intrathecal injection of morphine (control),  $\beta$ -endorphin levels measured in maternal venous blood samples differed

**Table 1.** Characteristics of Patients Given 1 mg of Morphine Intrathecally followed 1 hr later by an IV Bolus and Infusion of Naloxone or Saline<sup>a</sup>

	Intravenous saline <sup>b</sup> (n = 17)	Intravenous naloxone <sup>b</sup> (n = 23)
Primiparas (no. of patients)	9	13
Weight (kg)	69.1 ± 4.3	69.6 ± 5.4
Gestational age (wk)	39.7 ± 0.4	39.8 ± 0.3
Cervical dilatation before intrathecal injection of morphine (cm)	4.4 ± 0.4	4.9 ± 0.3
Augmentation of labor with oxytocin (no. of patients)	7	11
Fetal position at delivery (no. of patients)		
Occiput anterior	13	20
Occiput transverse	4	2
Occiput posterior	0	1
Duration of analgesia before delivery (min)	382 ± 57	269 ± 29

<sup>a</sup>No significant differences between the two groups.<sup>b</sup>Values are mean ± SEM.

significantly for the saline group ( $46.5 \pm 10.5$  fmol/ml) and the naloxone group ( $73.9 \pm 11.5$  fmol/ml). However, after intrathecal morphine, these concentrations decreased significantly below premorphine levels in both groups (Fig. 4). No significant difference existed between groups regarding the percent change from premorphine levels. For both groups, maternal levels increased at delivery to levels above those occurring before morphine: that is, to  $71.7 \pm 20.1$  fmol/ml with saline and to  $103.0 \pm 24.0$  with naloxone. However, these increases were not statistically significant.

### Maternal Side Effects

The incidence of maternal side effects is presented in Table 3. The incidence of pruritus was significantly lower in patients given intravenous naloxone than in those given intravenous saline. Vomiting, somnolence, dizziness, and urinary retention had a tendency to occur less frequently during labor and delivery in patients given naloxone; however, this was not statistically significant. There were no significant differences in severity of side effects between patients given naloxone and those given saline. The incidence of nausea was less than the incidence of vomiting because several patients vomited but denied being nauseous. No patient had evidence of respiratory depression. One patient in each group had a postdural puncture headache that was relieved by an epidural blood patch. After establishment of analgesia, no significant change occurred in maternal heart rate, blood pressure, respiratory rate, or venous PCO<sub>2</sub>.

Prior to delivery, 18 of the 23 patients in the naloxone group received only naloxone at an infusion rate of 0.4–0.6 mg/hr. Of the other five patients, one required additional intermittent boluses of naloxone,

two required promethazine (12.5 mg intramuscularly), one required both additional naloxone boluses and promethazine, and one delivered before the naloxone infusion could be started. The mean total naloxone dose prior to delivery was  $2.08 \pm 0.25$  mg. In some patients, as the rate of naloxone infusion was increased (to approximately 0.6 mg/hr) to treat side effects (especially, nausea and vomiting), analgesia was observed to decrease. By decreasing the rate of infusion, analgesia was again achieved. This is not reflected in the pain assessments because the changes in rates of naloxone infusion occurred between the set times of evaluation of pain intensity by the patient and investigator. Eight of 17 patients in the saline infusion group were given phenergan (12.5–25 mg) and/or diphenhydramine (15–20 mg) intramuscularly for side effects prior to delivery.

### Condition of Infant

Fetal heart rate and variability were not changed by intrathecal injection of morphine or intravenous bolus and infusion of naloxone. Administration of naloxone to the mother did not adversely affect the infant. No significant differences in umbilical-cord blood-gas values were found, except in the umbilical arterial blood samples. The umbilical artery pH and PO<sub>2</sub> values were significantly higher in the naloxone group ( $7.25 \pm 0.01$ ,  $20.5 \pm 1.2$  mm Hg) than in the saline group ( $7.21 \pm 0.02$ ,  $16.7 \pm 0.7$  mm Hg). There were no significant differences between groups on Apgar scores and NACs. At 1 min after delivery, 82% and 87% of infants of mothers given saline or naloxone, respectively, had Apgar scores of 7 to 10; and at 5 min, all had scores of 7 to 10. The TSR was less than 90 sec for all neonates of mothers given saline, and for all

**Table 2.** Progress of Labor, Method of Delivery, and Method of Anesthesia for Delivery for Patients Given 1 mg of Morphine Intrathecally, followed 1 hr later by an IV Bolus and Infusion of Saline or Naloxone

	Intravenous saline ( <i>n</i> = 17)	Intravenous naloxone ( <i>n</i> = 23)
First stage of labor (no. of patients)		
Normal progress of first stage	14	21
Slow slope active phase	2	1
Active phase arrest	1	1
Second stage of labor		
Mean duration (min) <sup>a</sup>	102.2 ± 22.9	73.7 ± 13.0
>120 min (no. of patients)	5	6
Method of delivery (no. of patients)		
Spontaneous	12	20
Vacuum extraction	0	1
Midforceps <sup>b</sup>	5	1
Cesarean section	0	1
Anesthesia for delivery (no. of patients)		
None	4	9
Local	7	7
Pudendal	1	5
Epidural	5	1
General	0	1

<sup>a</sup>Values are mean ± SEM. The patient in the naloxone group delivered by cesarean section is not included in the determination of the mean duration of the second stage of labor.

<sup>b</sup>Difference between groups of patients receiving saline or naloxone is significant at  $P < 0.05$ .

but one neonate of mothers given naloxone. At 15 min, 82% (saline) and 87% (naloxone) of infants had scores of 35–40 on the NACS. At 2 hr, 88% (saline) and 83% (naloxone) of neonates had scores of 35–40; and at 24 hr, all infants had scores of 35–40. At the time of delivery, mean plasma concentration of naloxone was  $1.92 \pm 0.28$  ng/ml in umbilical venous blood.  $\beta$ -endorphin concentrations in umbilical venous blood were not significantly different, i.e.,  $78.7 \pm 15.9$  and  $57.0 \pm 8.2$  fmol/ml for the saline and naloxone groups, respectively.

## Discussion

The intrathecal injection of morphine (1 or 2 mg) in normal saline has been reported to completely relieve the pain of labor, but with a high incidence of maternal side effects (2). In a previous study (3) we investigated whether even smaller doses of morphine, 0.5 mg or 1 mg, would relieve the pain of labor, and whether a hyperbaric solution of morphine would decrease the incidence of side effects. We found no significant difference in obstetric analgesia between the two doses, with both doses providing excellent analgesia for labor. We also found there was no difference in incidence of side effects when morphine was mixed in normal saline versus a hyperbaric dextrose solution.

Small doses of naloxone have reversed or alleviated the adverse side effects of epidurally or intrathecally

administered morphine without reversing analgesia (3,6,9). Naloxone competitively antagonizes the action of morphine at opiate receptor sites. After intrathecal administration of morphine, the concentration of morphine is much higher in the substantia gelatinosa of the dorsal horn of the spinal cord than in areas of the brain believed to mediate narcotic-induced side effects (i.e., the area postrema, the floor of the fourth ventricle, and the brainstem nuclei) (14). Because of the relatively smaller concentration of morphine in the brain, small doses of naloxone may be able to competitively displace morphine from the opiate receptors in the brain without affecting analgesia mediated by receptors in the spinal cord. In this study, we investigated whether the incidence of narcotic-induced side effects could be decreased by naloxone without also decreasing the analgesia. We also studied the effects of maternal naloxone administration on the condition of the newborn. This study may be considered limited because the investigators evaluating the occurrence of maternal side effects knew whether saline or naloxone was being administered. Patients in the saline group were not allowed to remain uncomfortable from side effects, rather, these patients were treated with promethazine or diphenhydramine prior to delivery. Naloxone was not administered to patients in the saline group prior to delivery because we wanted to compare infants whose mothers received naloxone with infants whose mothers did not, and to compare  $\beta$ -endorphin levels in



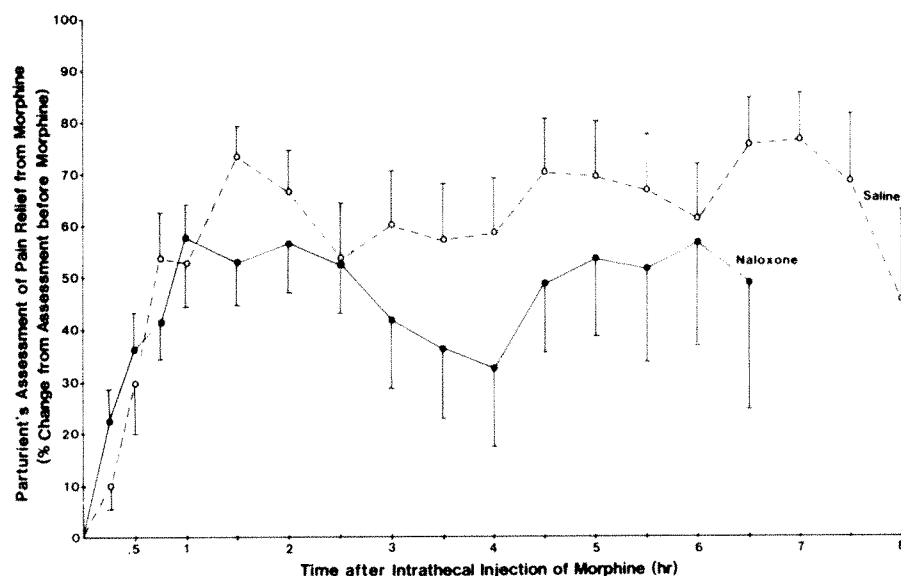


Figure 2. Maternal pain relief (before delivery) after intrathecal administration of 1 mg morphine followed 1 hr later by an intravenous bolus and infusion of saline (○—○) or naloxone (●—●). Data points represent averaged data for those patients undelivered at the time of assessment; bars indicate SEM.

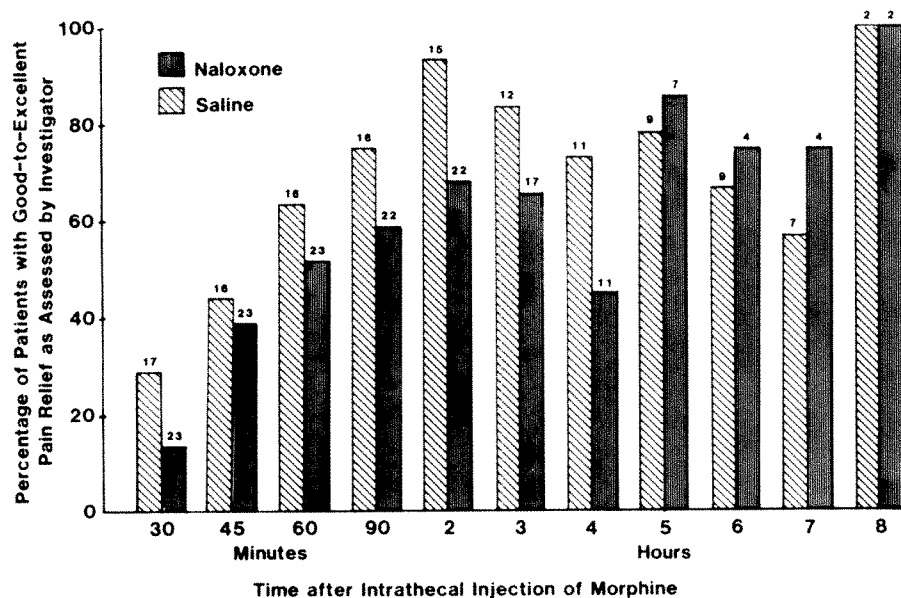


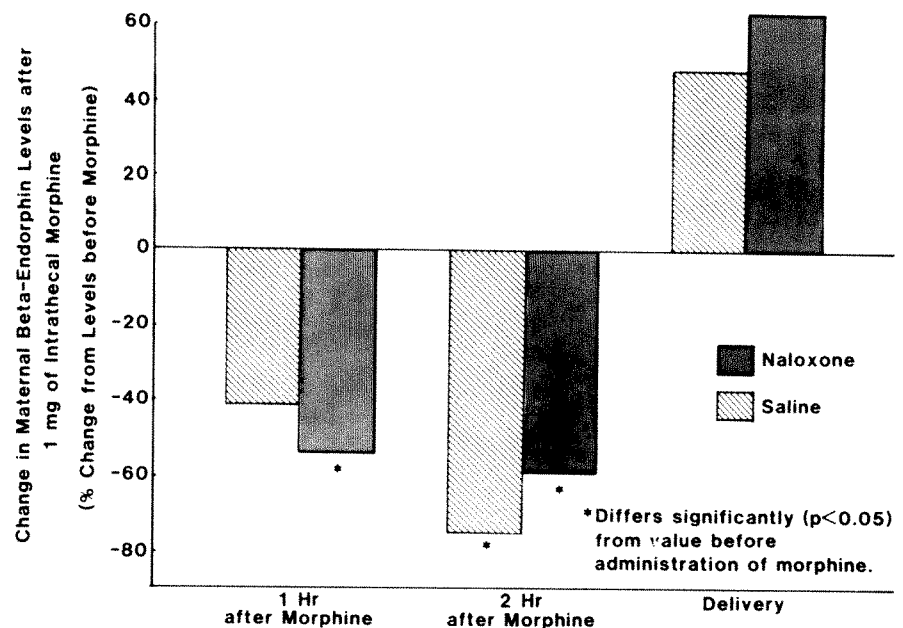
Figure 3. As assessed by independent investigators, percentage of patients having good-to-excellent pain relief after intrathecal administration of 1 mg of morphine followed 1 hr later by an intravenous bolus and infusion of saline or naloxone. Small numbers over bars represent the number of patients undelivered at the time of assessment.

patients who received naloxone and in patients who did not. Patients randomized to receive naloxone prior to delivery had the naloxone infusion increased before other medications were given. However, despite the possible bias of the investigator who knew to which group a patient was randomized, the naloxone infusion was found to have a very limited effectiveness for reducing side effects.

Compared with intravenous bolus followed by infusion of saline, intravenous bolus followed by infusion of naloxone 1 hr after intrathecal injection of morphine significantly reduced the incidence of pruritus without reducing analgesia. The incidences of vomiting, somnolence, dizziness, and urinary reten-

tion also decreased, but not significantly. There was no decrease in the incidence of nausea. It is possible that somnolence was related to relief of pain in parturients who were fatigued from labor and was not due to an effect of morphine on the central nervous system. Also, as the cervix dilates, many patients become nauseous or vomit; these responses may involve reflexes not affected by naloxone. In a previous study (3), we reported an incidence of pruritus of 94% after intrathecal injection of 1 mg of morphine. In the present study, the incidence of pruritus is lower, because patients who were observed rubbing their skin but who denied pruritus were not considered to have pruritus, as they were in the previous study.

Figure 4. Percentage change in maternal plasma  $\beta$ -endorphin levels from levels before morphine, 1 and 2 hr after intrathecal administration of 1 mg of morphine, and at delivery. An intravenous bolus and infusion of saline or naloxone were begun 1 hr after intrathecal morphine.



Intravenous administration of naloxone or saline was begun 1 hr after intrathecal injection of morphine to allow analgesia to develop, but before side effects occurred. Patients in the saline group had pruritus approximately 1.5 hr after intrathecal administration of morphine, and nausea and vomiting after 2 to 3 hr. Side effects occurred approximately 1 hr later in the naloxone infusion group. Side effects occur sooner after intrathecal administration of morphine than after epidural administration. Bromage et al. (15) administered 10 mg of morphine epidurally to healthy male volunteers. Pruritus began approximately 3 hr after epidural administration of morphine; nausea, 4 hr after administration; and vomiting, 6.3 hr after administration.

The administration of naloxone produced no apparent adverse effects on the fetus or neonate, despite placental transfer of the drug. Parenteral doses as high as 200  $\mu\text{g}/\text{kg}$  have been given to neonates without detectable adverse effects (16). In fact, the American Academy of Pediatrics recommends repeated intravenous bolus administration of naloxone, 10  $\mu\text{g}/\text{kg}$ , to infants suspected of narcotization (17). Studies conducted in fetal sheep show that naloxone (1 mg/kg) causes little change in fetal heart rate, blood pressure, arterial blood gases, and pH during normoxia (18). However, some case reports (19) and studies (20,21) suggest that naloxone may have a deleterious effect upon the asphyxiated human fetus or experimental animal. For example, naloxone (0.1–10 mg/kg) has been found to exacerbate hypoxic-ischemic brain injury in neonatal rats subjected to unilateral common

carotid artery ligation and hypoxia (21). The effects of naloxone on fetal circulatory responses to hypoxemia have also been studied in fetal sheep (18). Fetal sheep subjected to maternal hypoxemia responded with bradycardia and increase in blood pressure. After naloxone (1 mg/kg), the bradycardia increased by 10% and both combined ventricular output and placental blood flow decreased by 20%. However, in these studies, naloxone was administered directly to the fetus in doses much larger than used in our study.

We administered naloxone to the mother as a bolus of approximately 6  $\mu\text{g}/\text{kg}$  followed by an intravenous infusion of 6–9  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ . A loading dose of 0.2 mg of naloxone followed by naloxone infusion at the rate of 5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$  has been shown to prevent the reduction of the minute volume and decrease the elevation of  $\text{PET}_{\text{CO}_2}$  due to 4 mg of epidural morphine (22). After larger doses of naloxone, 0.4 mg/kg loading dose followed by 10  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ , minute volume and respiratory frequency have been shown to increase above control levels, and  $\text{PET}_{\text{CO}_2}$  to return to near control levels. Despite these findings, we still recommend close observation of patients for 24 hr after injection of intrathecal morphine even when an infusion of naloxone is used.

Pulmonary edema, severe hypotension, cardiac arrhythmias, and sudden death have been reported after naloxone reversal of the respiratory depressant effects of narcotics (23–26). These case reports have described patients who have received general anesthetics maintained primarily with narcotics and nitrous oxide in oxygen. In this study, we did not observe

Table 3. Percentages of Patients Having Adverse Side Effects during Labor and Delivery after Intrathecal Injection of Morphine followed by an IV Bolus and Infusion of Saline or Naloxone

	Intravenous saline (n = 17)	Intravenous naloxone (n = 23)
Pruritus <sup>a</sup>	41	9
Nausea	29	26
Vomiting	53	26
Urinary retention	59	39
Somnolence/dizziness	65	35
Respiratory depression	0	0
Headache	6	4

<sup>a</sup>Difference between groups of patients receiving saline or naloxone is significant at  $P < 0.05$ .

any significant changes in maternal heart rate and blood pressure following the intravenous bolus of 0.4 mg of naloxone 1 hr after intrathecal administration of morphine.

The endorphin system plays an important role in pain perception and response to stress.  $\beta$ -endorphin is released into the blood with ACTH by the pituitary during stress (27). Women in active labor have higher plasma concentrations of  $\beta$ -endorphins than do non-pregnant women or pregnant women not in labor, and these concentrations peak during delivery (27,28). Abboud et al. (29) studied the effects of epidural anesthesia on maternal plasma  $\beta$ -endorphin levels. Although these levels increased during labor, they decreased significantly after onset of epidural anesthesia. Our results were similar, regardless of group. Changes in plasma  $\beta$ -endorphin levels corresponded with changes in pain intensity and relief.  $\beta$ -endorphin levels decreased significantly 1 and 2 hr after intrathecal injection of morphine. However, at delivery,  $\beta$ -endorphin levels were equal to or higher than those measured before intrathecal administration of morphine. The physiologic significance of increased maternal plasma  $\beta$ -endorphin levels during labor and delivery, and their partial suppression by epidural and intrathecal analgesia remains unknown. Increases in plasma  $\beta$ -endorphin levels induced by stress are not associated with increases in brain or cerebrospinal fluid levels of  $\beta$ -endorphin (30,31). Infusion of naloxone had no apparent effect on release of  $\beta$ -endorphins by the pituitary into the blood in response to the stress of labor and delivery.

The use of intrathecal morphine for labor analgesia is limited by a number of factors including the following: delayed onset of analgesia; analgesia that is less profound than that achieved by epidural local anesthetics; analgesia that is not adequate for epis-

otomy or operative delivery; and a high incidence of maternal side effects. The purpose of this study was to evaluate the effectiveness of naloxone at reducing the incidence of side effects and the effects of maternal naloxone administration on the condition of the newborn. We conclude that the intrathecal administration of 1 mg of morphine, followed 1 hr later by a 0.4-mg bolus injection and an infusion (0.4 to 0.6 mg/hr) of naloxone, provided adequate analgesia for labor and significantly reduced the incidence of pruritus. The incidences of vomiting, somnolence, dizziness, and urinary retention were also reduced, but not significantly. This technique did not adversely affect the progress of labor, analgesia, or the clinical condition of the newborn. We do not advocate the routine use of a naloxone infusion in patients who receive intrathecal morphine. However, we suggest the administration of naloxone by infusion to patients in labor experiencing pruritus following the administration of intrathecal morphine.

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## Direct Opioid Application to Peripheral Nerves Does Not Alter Compound Action Potentials

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YUGE O, MATSUMOTO M, KITAHATA LM, COLLINS JG, SENAMI M. Direct opioid application to peripheral nerves does not alter compound action potentials. *Anesth Analg* 1985;64:667-71.

*The identification of opiate receptors on primary afferent fibers near the dorsal root ganglia suggests that opiates may be able to affect conduction in primary afferent nerve fibers. We examined the effect of directly applied, preservative-free morphine sulfate (0.1 mg/kg) and fentanyl citrate (25 µg/kg)*

*on the A beta, A delta, and C components of the compound action potential of the superficial radial nerve in decerebrate cats (n = 18). Neither drug caused any significant change in the area under the curve of any of the compound action potentials studied. These data indicate that systemically administered opiates are unlikely to cause changes in primary afferent nerve conduction.*

Key Words: ANALGESICS—morphine, fentanyl.

Prior to the early 1970s, it was widely assumed that opioids produced their analgesic effects by blocking pain signals in the brain, as well as by disrupting the affective component of pain. This view was shown to be too narrow when, in the early 1970s, three laboratories (1-3) independently reported that morphine was capable of blocking pain pathways at the level of the spinal cord as well. The importance of spinal opioid modulation of pain was demonstrated in animals in 1976 (4). The first of a large number of reports of human spinal opioid analgesia appeared in 1979 (5), and it finally established the functional significance of opioid analgesia occurring outside of supraspinal sites.

The potential for opiate actions outside of the CNS was demonstrated by the discovery of the presence of endogenous opiates and endogenous opiate receptors in neural and nonneural tissues of many mammalian species. In 1977, it was reported that morphine sulfate, when administered intraarterially, caused changes in the compound action potential of cat superficial radial nerve (6). In 1979, morphine was reported to cause changes in presynaptic excitability in single cutaneous afferent C and A fibers (7). In 1980, it was reported that opiate receptors exist on primary

afferent fibers in the area near the dorsal root ganglia (8). These findings challenged earlier reports (e.g., (9)) indicating that morphine failed to affect impulse transmission in mammalian nerve fibers.

The ability of spinally administered opioids to produce selective analgesia, as well as the possibility that opioids might act on peripheral afferent nerves, makes it important for us to be able to determine whether or not opioids are capable of either blocking or modulating nerve conduction in primary afferent fibers. This study was undertaken to determine whether the direct application of opioids on peripheral nerve fibers is capable of altering nerve conduction.

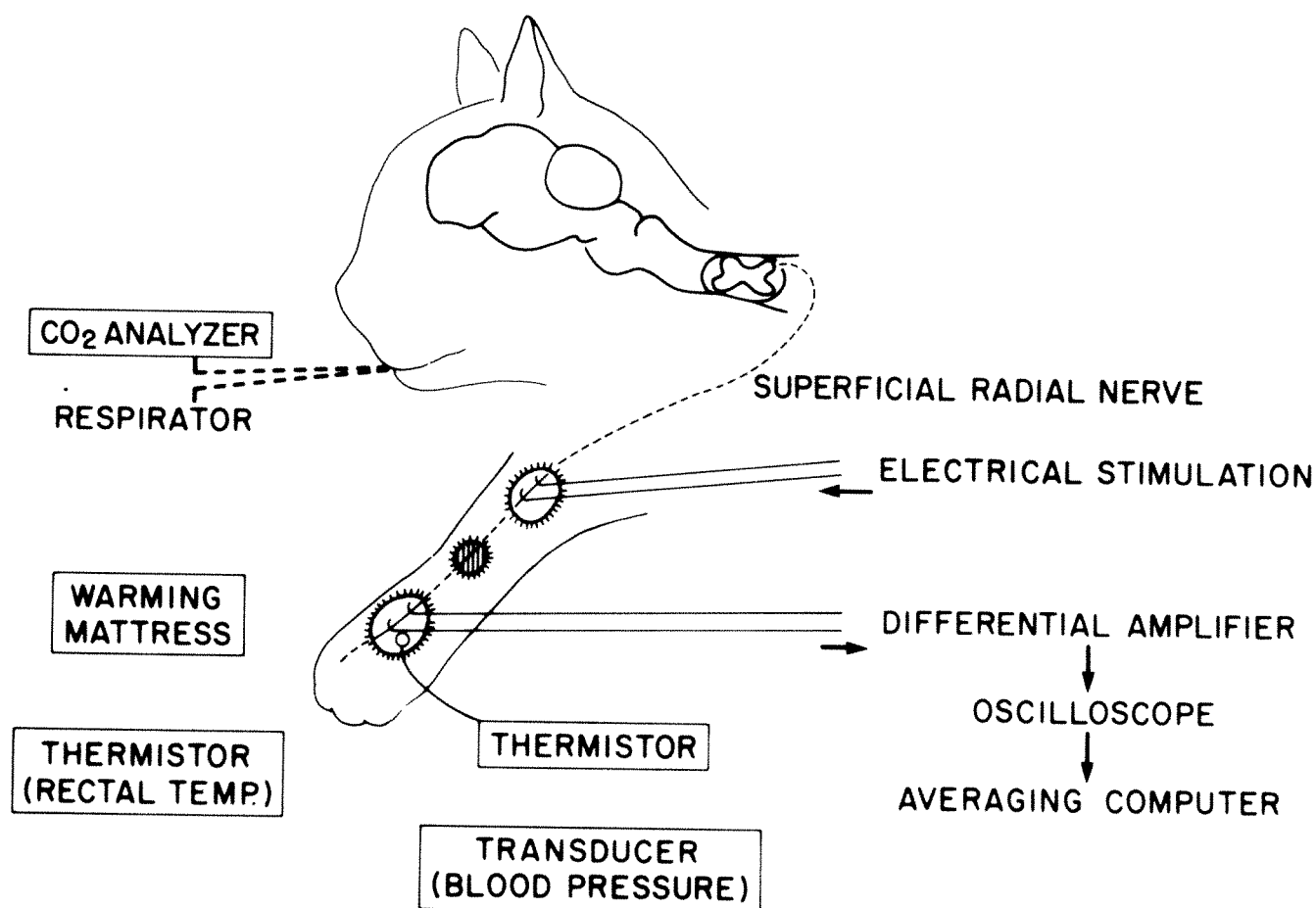
### Methods

All institutional, state, and federal guidelines for the use of research animals were carefully followed during all aspects of this study. Eighteen cats of either sex, weighing from 2.5 to 4.5 kg, were used in this study. Under halothane-nitrous oxide-oxygen anesthesia, a tracheostomy was performed, and a femoral artery and vein were cannulated for direct arterial blood pressure monitoring and intravenous fluid and drug administration. After placement in a Horsley-Clark stereotaxic apparatus, the animals were rendered decerebrate by electrolytic lesions in the midbrain reticular formation. Decerebration was produced so that general anesthesia could be discontinued, and opioid effects on primary afferents could be studied in pain-free, anesthetic-free, unconscious

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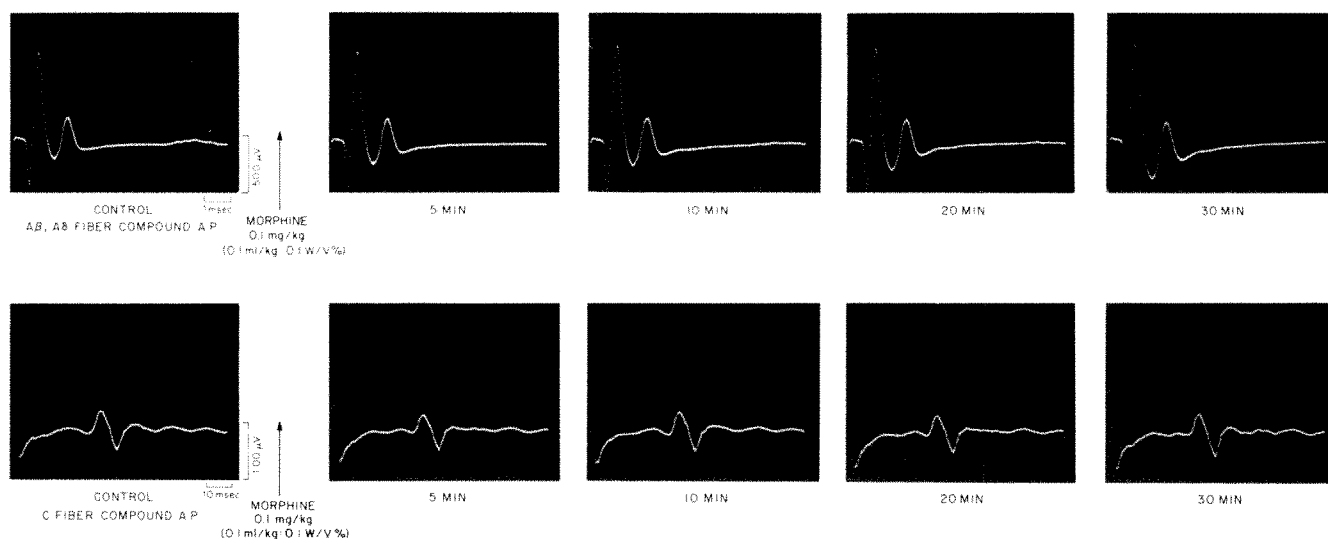


**Figure 1.** Diagrammatic representation of animal preparation. Decerebrate animals with carefully monitored and maintained physiologic parameters were used. The three sites of exposure of the superficial radial nerve are shown. Nerve stimulation was applied in the proximal site. Compound action potentials were recorded in the distal site. Drugs were administered in the middle site (cross-hatched area).

animals. The animals were ventilated with 100% oxygen using a volume-cycled ventilator connected to a nonrebreathing system. Ventilation was initiated immediately after the beginning of an intravenous infusion of lactated Ringer's solution containing 0.1% gallamine triethiodide ( $4-8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ). End-tidal  $\text{CO}_2$  was maintained between 4 and 5%. Systolic arterial blood pressure was maintained above 100 torr by the administration of lactated Ringer's solution, if necessary. Rectal temperature was maintained at  $37^\circ \pm 1^\circ \text{C}$  with an infrared heating lamp and a thermal servocontrolled water mattress.

The superficial radial nerve was exposed in three sites on the forelimb of each animal. The skin around each exposure site was mounted on a small metal ring

(Fig. 1) that was used to elevate the skin slightly, and thus produce a small well through which access to the nerve could be gained. The nerves were prepared for stimulation and recording by the placement of two pairs of silver bipolar electrodes. One pair was placed in the proximal pool on the animal's limb, and was used for stimulating the superficial radial nerve. The second pair of electrodes was placed on the nerve in the distal pool, and was used for recording the compound action potential. The proximal site for stimulation, and distal for recording, were used because of ease of equipment location. The nerve from which recordings were made is a sensory nerve, and the events responsible for conduction are similar for both orthodromic and antidromic activation. Each pair of electrodes was shielded from the surrounding tissue by a small piece of paraffin film. After placement of the electrodes in the proximal and distal wells, warm paraffin oil was applied to the nerve in each well in order to protect it from cooling and drying. Paraffin oil was maintained at a temperature of  $35^\circ \pm 0.5^\circ \text{C}$ . The center well, which was located between the proximal and distal wells, and which was used for drug



administration, was sealed with paraffin film to retain moisture and body temperature.

Electrical stimulation consisted of single rectangular pulses of 0.05 msec duration. Threshold intensities and the intensity required for maximum activation of A beta, A delta, and C fiber components of the compound action potential were determined in each animal. Compound action potentials were amplified, displayed on a cathode ray oscilloscope, and stored and averaged on a Nicolet model 1074 instrument computer. Sixteen consecutive responses were averaged for each test period. The areas under the compound action potential curves of the A beta, A delta, and C fiber components of the compound action potentials were determined by measuring the negative component of each of those potentials. A minimum of one hour separated the termination of the administration of the inhalation anesthesia from the beginning of neuronal recording. Either morphine sulfate, fentanyl citrate, or physiologic saline was tested only once in each animal.

After a determination of threshold intensities and the intensity required for maximum activation of the various components of the compound action potential, morphine sulfate (0.1 mg/kg in a volume of 0.1 ml/kg, 0.1% wt/vol, pH 6.5,  $n = 6$ ) or fentanyl (25  $\mu$ g/kg in a volume of 0.1 ml/kg, 0.025% wt/vol, pH 6.5,  $n = 6$ ) or physiologic saline (0.5 ml, pH 6.5,  $n = 6$ ), all at 37°C, was administered directly onto the superficial radial nerve in the middle well through the paraffin membrane covering that well. After drug or saline administration, A beta, A delta, and C fiber compound action potentials were measured every 5 min for 30 min. Student's *t*-test was used to determine

Figure 2. The effects of directly applied morphine sulfate (0.1 mg/kg, 0.1 wt/vol %, 0.1 ml/kg, pH 6.5) on the compound action potentials of cat superficial radial nerve. Recordings of the A beta and A delta components are shown in the upper row. The lower row presents the C fiber component. Each tracing is the average of 16 consecutive responses of the nerve to supramaximal electrical stimulation. Morphine produced no significant changes in the area under any of the components of the compound action potential.

Table 1. Effect of Morphine<sup>a</sup> on Mean Area Under the Compound Action Potentials Curve<sup>b</sup>

	5 min	10 min	20 min	30 min
A beta	98.5 $\pm$ 5.7	98.6 $\pm$ 8.0	98.2 $\pm$ 7.5	98.0 $\pm$ 7.2
(n)	(6)	(6)	(6)	(6)
A delta	98.0 $\pm$ 7.4	98.0 $\pm$ 5.2	95.6 $\pm$ 8.5	99.3 $\pm$ 11.0
(n)	(6)	(6)	(6)	(6)
C	97.3 $\pm$ 9.0	93.5 $\pm$ 10.4	95.8 $\pm$ 8.0	90.4 $\pm$ 10.0
(n)	(6)	(6)	(6)	(6)

<sup>a</sup>0.1 mg/kg, 0.1 % wt/vol, 0.1 ml/kg.

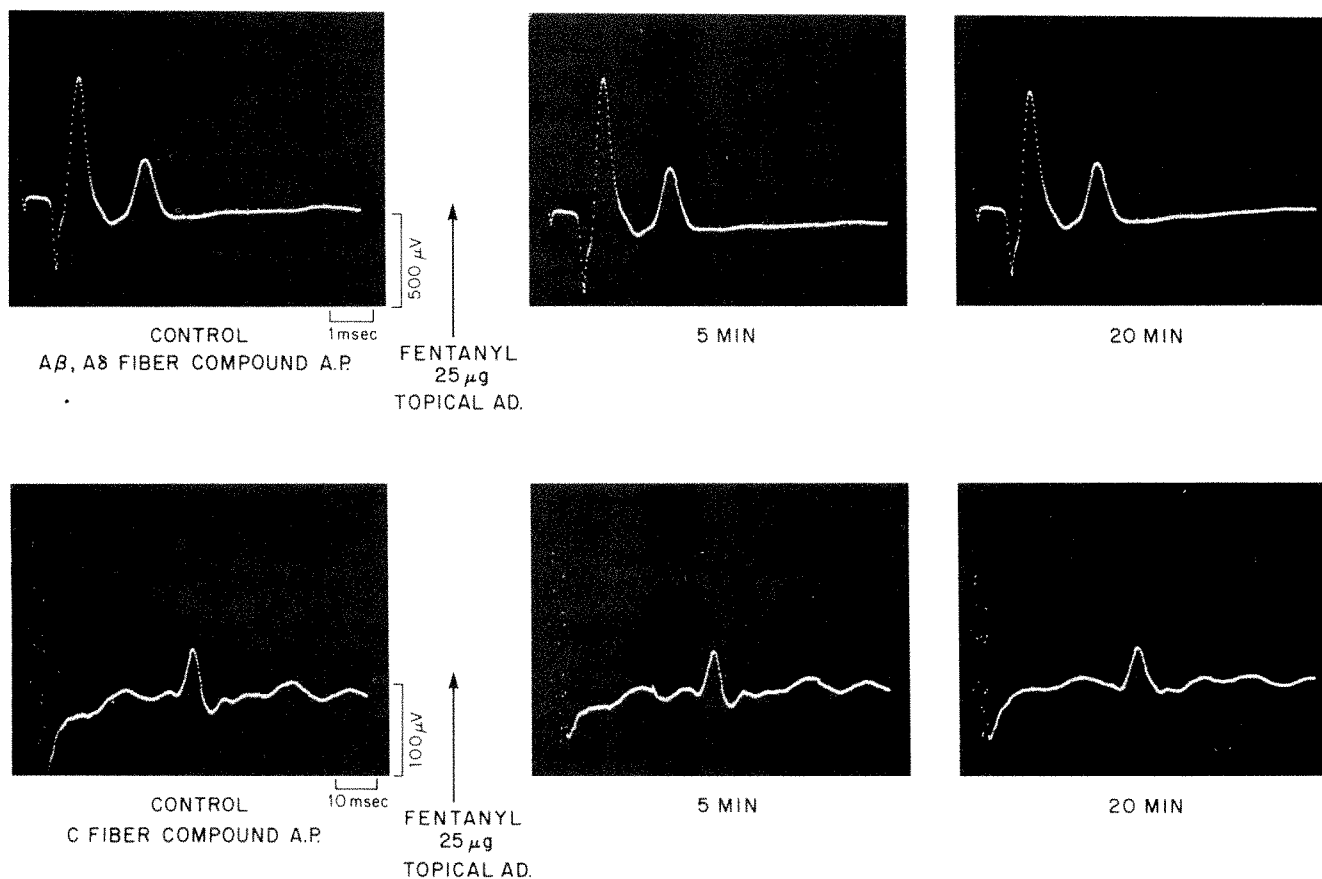
<sup>b</sup>Values represented as mean percent of control  $\pm$  SD.

statistical significance. *P* values less than 0.05 were considered significant.

## Results

### Morphine

The thresholds for the A beta, A delta, and C fiber components of the compound action potential of the fibers in which morphine was studied were 0.2–0.35 V, 3.0–4.0 V, and 30–40 V, respectively. Conduction velocities of the three fiber types were: A beta fibers, 62.3  $\pm$  1.8 m/sec (mean  $\pm$  SD); A delta fibers, 22.4  $\pm$  4.2 m/sec; and C fibers, 1.6  $\pm$  0.4 m/sec. Examples of A beta, A delta, and C fiber components of a com-



**Figure 3.** Effects of directly applied fentanyl ( $25 \mu\text{g/kg}$ ,  $0.025\%$  wt/vol  $0.1 \text{ ml/kg}$ , pH 6.4) on the compound action potentials of cat superficial radial nerve. Recordings of the A beta and A delta components are shown in the upper row. The lower row presents the C fiber component. Each tracing is the average of 16 consecutive responses. Fentanyl produced no significant changes in the area under any of the components of the compound action potential.

onstrates the lack of effect of  $25 \mu\text{g/kg}$  of fentanyl applied directly onto the superficial radial nerve. Table 2 presents the mean area of the compound action potential expressed as a percent of control 5, 10, 20, and 30 min after the direct application of fentanyl to the superficial radial nerve.

compound action potential of a cat sural nerve prior to, and after morphine administration are shown in Figure 2; note the lack of morphine effect. Table 1 presents the mean area of the compound action potentials expressed as a percent of control 5, 10, 20, and 30 min after the direct administration of morphine sulfate (resulting in no change) to the superficial radial nerve.

### Fentanyl

The threshold for the A beta, A delta, and C fiber components of the compound action potentials recorded in the fentanyl study were  $0.2\text{--}0.4 \text{ V}$ ,  $2.5\text{--}3.5 \text{ V}$ , and  $40\text{--}50 \text{ V}$ , respectively. The conduction velocities were  $60.6 \pm 2.2 \text{ m/sec}$  (mean  $\pm$  SD) for the A beta fibers,  $21.6 \pm 4.4 \text{ ms/sec}$  for the A delta fibers, and  $1.7 \pm 0.3 \text{ m/sec}$  for the C fibers. Figure 3 dem-

### Saline

No significant difference was noted between the effects of physiological saline and the effects of either morphine or fentanyl.

### Discussion

The three most recent editions of *The Pharmacologic Basis of Therapeutics* by Goodman and Gilman (10) clearly state the current belief concerning the action of opioids on nerve conduction: "The opioids . . . do not impair the conduction of the nerve impulse along peripheral nerves." It has been assumed that opiate effects, at least as they relate to analgesia, are associated with an effect within the central nervous system rather than in the periphery. This assumption, however, was challenged by a report by Jurna and Grossmann



Table 2. Effect of Fentanyl<sup>a</sup> on Mean Area under the Compound Action Potentials Curve<sup>b</sup>

	5 min	10 min	20 min	30 min
A beta	97.4 ± 6.4	92.0 ± 8.7	93.8 ± 9.4	94.2 ± 4.3
(n)	(6)	(6)	(6)	(6)
A delta	96.7 ± 5.5	90.2 ± 11.4	96.2 ± 8.5	91.8 ± 10.4
(n)	(6)	(6)	(6)	(6)
C	91.0 ± 11.3	89.0 ± 10.9	88.8 ± 12.3	90.2 ± 9.2
(n)	(6)	(6)	(6)	(6)

<sup>a</sup>25 µg/kg, 0.025% wt/vol, 0.1 ml/kg.<sup>b</sup>Values expressed as mean percent of control ± SD.

(6) that "... the intraarterial administration of morphine (2 mg/kg) to the sural nerve in situ ... increased the compound action potential of the A beta fibers and reduced that of the A delta and C fibers of the nerve." The discovery of endogenous opiates and endogenous opiate receptors, and, more importantly, the discovery of opiate receptors on peripheral nerves near the dorsal root ganglia (8) raised the possibility that systemically administered opioids produce part of their effect by altering nerve conduction in the periphery. This question is particularly important in light of the possible site of action of opiates on peripheral nerves following either epidural or spinal application. It is also of importance because of the potential clinical use of regional nerve block using opioids with the possible ability to obtund pain fibers without influencing other sensory, motor, or autonomic fibers.

The results of the present study support earlier research that indicates that opioids are not capable of blocking nerve conduction in primary afferent fibers at concentrations that are likely to be achieved after systemic administration. The difference between the results obtained in this study and those reported by Jurna and Grossmann are likely to be due to differences in concentration of opioids studied. Major effects reported by Jurna and Grossmann (6) followed intraarterial injection, which may have produced much higher local concentrations near the nerve fibers, resulting in a block due to a nonspecific local anesthetic effect of the drug, rather than a specific interaction with opiate receptors. Another difference in technique that may have influenced the results is that Jurna and Grossmann cut the nerve distal to the recording site. In our study the nerve was left intact.

The use of a cut nerve preparation, as was done by Jurna and Grossmann, may produce different results.

While the results of the present study indicate that systemically administered opioids are not likely to block conduction in the conducting portion of axons, it does not eliminate the possibility that opiates are capable of blocking neuronal activity by interacting at sites located on the receptor portion of primary afferent fibers. Nor does it disprove the possibility that opiate receptors on primary afferent fibers near the dorsal root ganglia are influenced by levels of opioids normally achieved systemically, or after spinal or epidural administration. Another question that is not directly addressed in the study is whether the lack of effect seen was due to absence of appropriate receptors on the axons or inability of the drugs to penetrate permeability barriers (e.g., perineurium). Fentanyl was specifically used in this study to attempt to address this issue, and we feel that its high lipid solubility would allow fentanyl access to neural membranes, but we have no direct proof that such access was available. Further studies are required to answer some of these additional questions.

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## A Multicenter Study of the Epidemiology of Hepatitis B in Anesthesia Residents

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BERRY AJ, ISAACSON IJ, KANE MA, et al. A multicenter study of the epidemiology of hepatitis B in anesthesia residents. *Anesth Analg* 1985;64:672-6.

*Practicing anesthesiologists are at high risk of hepatitis B infection, but the risk for anesthesia residents has not been assessed. Anesthesia residents at seven universities were surveyed to study the epidemiology of hepatitis B in these trainees. Hepatitis B virus markers in serum were measured and data from questionnaires were used to determine characteristics of anesthetic practice, effectiveness of strategies for hepatitis B virus infection control, and nonvocational hepatitis B risk factors. Of 267 participants, 12.7% (range*

*of the seven centers, 8.7%-22.7%) had serum markers for hepatitis B virus. The seropositivity (17.8%) in anesthesia residents who had completed more than 12 months of non-anesthesia postgraduate clinical training, or who had practiced medicine in another specialty prior to anesthesia, was greater than in the other trainees (9.4%). Based on their risk and the ineffectiveness of current control measures, anesthesia residents who lack hepatitis B virus immunity should be vaccinated prior to or as early as possible in their training.*

Key Words: LIVER—hepatitis.

In previous surveys, anesthesiologists have been shown to be at significant risk of hepatitis B virus (HBV) infection (1-3). Berry et al. demonstrated that the prevalence of positive serologic markers for HBV was high (17%) in a group of university affiliated anesthesiologists in practice for less than five years (4). In a study conducted at a midwest medical school, 5.4% of students had antibodies to HBV surface antigen (anti-HBs) (5). Taken together, these data suggest a substantial risk of HBV infection during residency training. If anesthesia residents have a prevalence of HBV serum markers greater than medical students, the hepatitis B (HB) vaccine (6,7) should be recom-

mended to these individuals prior to or early in their specialty training. We surveyed anesthesia residents at seven university medical centers to determine the prevalence of HBV serologic markers, the effectiveness of prior strategies for HBV infection control, and the need for vaccination in these trainees.

### Methods

After receiving approval from the Institutional Review Board of seven university medical centers (University Hospitals of Cleveland, Emory University, Pennsylvania State University, Northwestern University, Stanford University, University of California at Los Angeles, and University of California at San Francisco), we contacted all anesthesia residents in these training programs and obtained blood samples from consenting residents. Each resident participating in this study completed a questionnaire covering personal historical data, duration and type of medical practice prior to entering anesthesia training, non-occupational risk factors for HBV infection, current efforts to prevent HBV infection, and characteristics of their anesthesia practice. The confidentiality of the individual's serologic status and questionnaire re-

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Received from the Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia; Hepatitis Branch, Viral Diseases Division, Centers for Disease Control, Atlanta, Georgia; University of California at San Francisco, San Francisco, California; University Hospitals of Cleveland, Cleveland, Ohio; University of California at Los Angeles, Los Angeles, California; Pennsylvania State University School of Medicine, Hershey, Pennsylvania; Max Kade Foundation and Stanford University School of Medicine, Palo Alto, California; and Northwestern University, Chicago, Illinois. Accepted for publication February 13, 1985.

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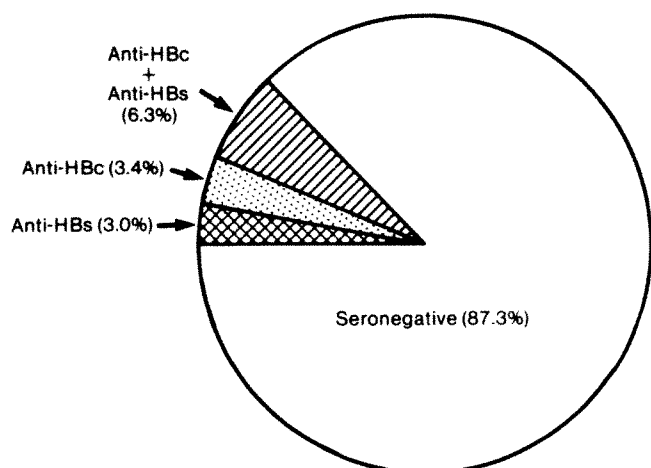


Figure 1. The prevalence of serologic markers of hepatitis B virus in 267 anesthesia residents at seven university centers. Anti-HBs, hepatitis B surface antibody; anti-HBc, hepatitis B core antibody.

sponses were assured by the use of coded blood samples, questionnaires, and data sheets with the identifying numbers known only to the participant.

Radioimmunoassays (RIA) (Abbott Laboratories, North Chicago, IL; use of commercial names is for identification only and does not imply endorsement by the Public Health Service or the US Department of Health and Human Services) were used to determine the presence of HBV surface antigen (HBsAg), HBV surface antibody (anti-HBs), and HBV core antibody (anti-HBc) in the serum samples. Seropositivity was defined as the presence of at least one of these serum markers of HBV. Individuals who were anti-HBc negative but had borderline positive anti-HBs (less than ten sample ratio units when performed by RIA) were considered seronegative. Data from individuals who had received hepatitis B immune globulin within the six months prior to study or the hepatitis B vaccine were removed from further analysis regardless of the serologic status.

Data were analyzed using Pearson correlation coefficient, linear regression analysis, Yates corrected  $\chi^2$ , or Fisher's exact test. Statistical significance was accepted at a  $P < 0.05$  and  $P$  values are given where appropriate.

## Results

Two hundred-ninety individuals or 83.3% of all residents in the seven training programs volunteered to take part in the study. Information from the questionnaire indicated that 17 residents consenting to participate had already received HB vaccine and six had been given hepatitis B immune globulin within

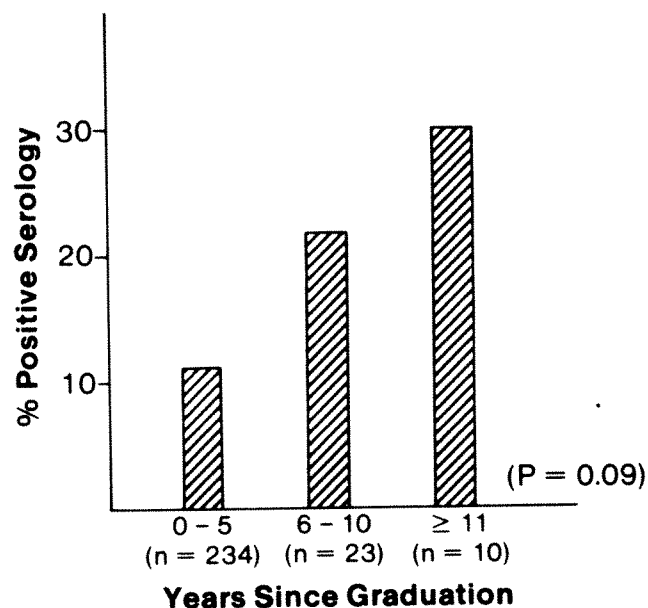


Figure 2. The prevalence of serologic markers of hepatitis B virus in anesthesia residents grouped by years since graduation from medical school.

six months of this survey. In these 23 residents, both the HB vaccine and hepatitis B immune globulin were likely to produce anti-HBs positivity that would reduce these individuals' time at risk for HBV infection, and therefore serologic and epidemiologic data from them were not included. The following results are based on the remaining 267 participants.

The overall prevalence of seropositivity was 12.7% with no statistically significant difference among the seven institutions (range at the seven centers, 8.7%–22.7%). Figure 1 indicates the distribution of HBV serum markers. The prevalence in male (12.8%) and female (13.1%) residents was similar, and there was no correlation between seropositivity and age. The majority of the participants were white (89.3%), and the difference in seropositivity between whites (11.5%) and nonwhites (21.4%) was not statistically significant. The prevalence of seropositivity increased with years since graduation from medical school, and although not statistically significant ( $P = 0.09$ ), this trend seems clear (Fig. 2).

In 107 residents who had completed more than 12 months of nonanesthesia postgraduate clinical training (mean 33.1 months; range 13–99), or who had practiced medicine in another specialty prior to entering anesthesia (mean years in practice, 3.0; range, 1–18), the prevalence of serum markers of HBV was 17.8%. Emergency room duty was the most common area of the previous practice (51%), followed by internal medicine (16%), and general practice (12%).

Table 1. Use of Gloving in Anesthesia Residents

	Years since graduation from medical school			
	0-5	6-10	>10	Total
High exposure	27(11.6%)	7(30.4%)	3(30%)	37
Low exposure	206(88.4%)	16(69.6%)	7(70%)	229
Total	233	23	10	266

(P = 0.01)

High exposure, never wore gloves or wore them only during sterile procedures.

Low exposure, always wore gloves or wore them during contact with patients thought to be capable of transmitting hepatitis.

Gloving practice in one participant was unknown.

The 9.4% seropositivity rate in the 160 residents who had 12 months or less of a clinical base year and no prior medical practice was significantly less than that of the former group. There was no difference in prevalence of HBV markers with duration of anesthesia training in either of these two groups.

Twenty-four (70.6%) of the 34 residents with serum markers of HBV had no knowledge of prior hepatitis, and presumably had asymptomatic infection. There was no correlation between seropositivity and prior blood transfusion, tattoos, intravenous drug use, or homosexual activities. Although 74% of the participating residents routinely performed a preoperative chart review of patients they were to care for, and 83% specifically questioned patients in an attempt to determine the HBV carrier status of their patients, these efforts were not associated with a lower prevalence of seropositivity. Based on whether residents routinely used gloves when taking care of patients, participants were divided into two groups: high exposure (never wore gloves or wore them only during sterile procedures) or low exposure (always wore gloves or wore them during contact with patients thought to be capable of transmitting hepatitis). Although the low exposure group had a lower seropositivity (11.4%) than the residents with high exposure (21.6%;  $P = 0.11$ ), the analysis was confounded by a third variable. This variable was the fact that a greater percentage of residents who had graduated from medical school more than six years prior to this study were in the high exposure group ( $P = 0.01$ ) (Table 1). Therefore, the difference in HBV seropositivity cannot be definitely attributed to gloving practices but may reflect the increased seropositivity found in the earlier graduates (Fig. 2).

Only 19.0% of the 290 residents surveyed had been vaccinated or planned to receive the HB vaccine when queried at the time of the study. Of the 233 seronegative residents (i.e., those at risk for HBV infection), 69 (29.6%) did not plan on vaccination while 132 (56.7%) were undecided (Table 2).

Table 2. Plans for HB Vaccination<sup>a</sup>

	Seropositive	Seronegative	Total
Yes	4	32	36(13.5%)
No	13	69	82(30.7%)
Undecided	17	132	149(55.8%)
Total	34	233	267

<sup>a</sup>Excludes 17 participants who had received HB vaccine and 6 who had received hepatitis B immune globulin.

## Discussion

These data collected from seven university medical centers indicate that anesthesia residents are at high risk for HBV infection. We studied residents from institutions in different geographic locations in rural and metropolitan areas in order to sample individuals exposed to diverse patient populations. Anesthesia departments that had previously offered HB vaccination programs to residents were not included in this study. Geographic location and patient population did not appear to be a predictive factor because the seropositivity did not differ statistically by institution.

The prevalence of HBV serum markers in residents without prior medical practice and with less than one year of nonanesthesia postgraduate training (9.4%) was greater than the value reported for medical students (5.4%) (5) and less than that for anesthesia faculty (23.3% (1) and 17% (2)). The exposure of anesthesia residents to HBV infection during training is not unexpected because they undoubtedly contact patients who are infectious for HBV. Anesthesia residents who had previously been in other medical specialties had a higher prevalence of HBV seropositivity (17.8%) than residents who had less nonanesthesia clinical experience. The greater time at risk for HBV infection during prior practice was probably responsible for the increased seropositivity. Half of the resident group with the greater amount of nonanesthesia clinical experience had been emergency room physicians, a specialty known to be at increased risk of HBV infection (8).

Seropositivity increased with years since medical school graduation (Fig. 2), but it must be realized that this time included periods of nonanesthesia medical training and practice. Although the incidence (new cases per year) of HBV infection in anesthesiologists cannot be calculated from the present study, the annual attack rate appears to be sufficiently low, so that it is unlikely that the prevalence of HBV seromarkers would increase significantly over the three years of residency. In fact, it did not increase with the duration of anesthesia training.



Residents' attempts to reduce HBV infection by identifying carriers through routine chart review of patients to be cared for or patient questioning were unsuccessful because seropositivity was not reduced by these efforts. HBV carriers are often asymptomatic and unaware of their disease. Routine preoperative laboratory tests do not include HBsAg testing and thus are also not sufficient for diagnosing HBV carriers. A study conducted at a large general hospital demonstrated that 1.3% of adult patients without clinical evidence of hepatitis were HBsAg-positive on serologic examination (9). Anesthesia residents may be infected when caring for these patients in the operating room, intensive care unit, or hospital wards.

The use of gloves during contact with all patients, or those thought to be acutely infected or to be HBV carriers did not correlate with decreased HBV seropositivity when gloving was used to attempt to control HBV infection. There are several explanations for the lack of effectiveness of gloving. As stated previously, all HBV carriers are not identified preoperatively, and therefore gloves are not used during contact with all patients capable of transmitting HBV. Infection will not be prevented when a glove is accidentally penetrated by a needlestick. Blood, saliva, and certain other body fluids are potential vehicles for transmitting HBV through breaks in skin or mucous membranes not protected by gloves (10). In addition, HBV continues to be infectious for at least one week in dried blood on environmental surfaces (11). Infection could therefore occur after removal of gloves by contact with blood carrying HBV that is left on equipment in the operating room.

A hepatitis B vaccine for active prophylaxis has been developed. The Immunization Practices Advisory Committee (ACIP) of the Centers for Disease Control has recommended the use of this vaccine for health care workers with a significant risk of HBV infection (7). This three-dose vaccine induces the production of significant serum levels of anti-HBs and is highly effective in preventing HBV infection. Information collected from epidemiologic surveillance confirms the vaccine's safety (12). To minimize the overall cost of vaccination of large groups, several investigators have published analyses of the cost effectiveness of prevaccination screening for HBV serum markers to identify immune individuals who do not require active immunization (7,13). Based on the current cost of the HB vaccine, screening prior to vaccination is cost effective only if it is anticipated that a sufficient number of potential vaccine recipients are already seropositive. Considering the prevalence data from the present study, at some institutions the cost

of laboratory tests, the HB vaccine, and administration of the vaccine would warrant the prevaccination screening of anesthesia residents who have completed more than 12 months of nonanesthesia postgraduate training or who have previously practiced in another specialty. Residents entering anesthesia training without direct patient care experience, who are likely to have a lower prevalence of seropositivity, should probably be vaccinated without prior screening programs.

We have demonstrated that previous strategies for HBV infection control such as the use of gloves and routine attempts to identify hospitalized HBV carriers are not associated with reduced HBV seropositivity. Because the risk of hepatitis B is significant in anesthesia residents, we recommend vaccination of individuals prior to or as soon as possible after entering anesthesia training programs. Most residents were undecided or did not plan to receive the hepatitis B vaccine when polled during this survey. The reasons for the residents' reluctance to accept vaccination cannot be determined from our data. However, educational efforts are indicated to inform residents of their risk of HBV infection and its potential chronic sequelae, and of the efficacy and safety of HB vaccine.

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## Effects of Halothane and Fentanyl Anesthesia on Plasma $\beta$ -Endorphin Immunoreactivity during Cardiac Surgery

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CORK RC, HAMEROFF SR, WEISS JL. Effects of halothane and fentanyl anesthesia on plasma  $\beta$ -endorphin immunoreactivity during cardiac surgery. *Anesth Analg* 1985;64:677-80.

*We studied the effects of halothane anesthesia ( $n = 6$ ) and fentanyl anesthesia ( $n = 9$ ; 50-100  $\mu\text{g/kg}$ ) on plasma  $\beta$ -endorphin immunoreactivity as a measure of stress response during coronary artery bypass grafting, including cardiopulmonary bypass. Plasma levels of  $\beta$ -endorphin im-*

*munoreactivity measured prior to induction, after induction, after intubation, after skin incision, during cardiopulmonary bypass, and on leaving the operating room were significantly higher in patients given halothane during cardiopulmonary bypass and on leaving the operating room than they were in patients given fentanyl.*

**Key Words:** ANESTHESIA, CARDIAC. ANESTHETICS, VOLATILE—halothane. ANESTHETICS, INTRAVENOUS—fentanyl. PEPTIDES— $\beta$ -endorphin.

Plasma levels of  $\beta$ -endorphin immunoreactivity (IR) are known to reflect stress response to such noxious stimuli as foot shock (1), respiratory distress (2), laryngoscopy and intubation (3), and surgery (4). The pituitary and hypothalamus mediate the response of the body to stress (5), and high concentrations of opiate receptors have been located in the pituitary and hypothalamus (6). Although the correlation of organ function to location of opiate receptors does not by itself imply a causal link, it has been shown that exogenous opiates do reduce the body's response to stress as measured by plasma levels of cortisol (7), growth hormone (8,9), glucose (10), ADH (11-13), and catecholamines (11,12).

Many of these studies have compared halothane anesthesia with fentanyl anesthesia in altering stress responses. None, however, have studied plasma levels of  $\beta$ -endorphin IR. The purpose of this study was to compare the effects of fentanyl and halothane on plasma  $\beta$ -endorphin immunoreactivity as a measure of the stress response during cardiac surgery and cardiopulmonary bypass.

### Methods

With informed consent and approval by the Human Subjects Committee, 15 male patients scheduled for

coronary artery bypass graft surgery were studied. Premedication consisted of 0.4 mg scopolamine and 0.1 mg/kg morphine intramuscularly. Patients were randomly assigned (by the flip of a coin) to receive either halothane (the halothane group) or fentanyl (the fentanyl group). Halothane induction was accomplished with 60% nitrous oxide and 0.5 to 4% halothane, and anesthesia was maintained with 0.7 to 1.5% halothane and oxygen. Fentanyl was given as a bolus at induction. The dose of fentanyl varied between 50  $\mu\text{g/kg}$  and 100  $\mu\text{g/kg}$ , depending on the anesthesiologist responsible for the case. A specific induction dose was not a controlled part of the protocol. Transtracheal anesthesia with 4 ml of 4% lidocaine was administered to both groups prior to tracheal intubation, and 10-30 mg diazepam was given to all patients prior to cardiopulmonary bypass (CPB). During CPB, no halothane was administered. After CPB, halothane was administered again in the halothane group as tolerated by each patient.

Peripheral arterial blood samples were obtained for measurement of plasma  $\beta$ -endorphin IR after all lines had been placed and the patient was resting comfortably (baseline), after induction of anesthesia immediately prior to intubation, 2 min after endotracheal intubation, 2 min after skin incision, at the start of rewarming while on CPB, and as the patients were leaving the operating room for the cardiothoracic intensive care unit. At the same times as the blood samples, measurements of nasopharyngeal temperature, systolic and diastolic blood pressures, and heart rate were made. Additional data included patient age,

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weight, height, amount of pump prime, pump flow, amount of diazepam administered, anesthetic time, and bypass time.

Measurement of plasma  $\beta$ -endorphin IR was done after 10 ml of blood was collected in prechilled polypropylene tubes containing 100  $\mu$ l of a solution of bacitracin (2 mg/ml) and EDTA (20 mM). The whole blood was then separated by centrifugation at 3000 RPM for 10 min at 4°C. The plasma was removed to a second polypropylene tube and stored at -80°C until analysis. Prior to analysis, plasma samples were lyophilized and reconstituted to one-third their original volume.  $\beta$ -endorphin IR was measured in unextracted concentrated samples by radioimmunoassay (New England Nuclear). Assay sensitivity was 5 pg/ml. The interassay coefficient of variation was 12.7%; the intraassay coefficient of variation was 83% (14). Student's *t*-test for grouped data was used to compare the fentanyl group with the halothane group. Statistical significance was defined as  $P < 0.05$ .

## Results

Six patients received halothane and nine received fentanyl (Table 1). No significant between-group differences were observed for age, weight, height, amount of pump prime, pump flow, amount of diazepam administered, and duration of anesthesia and CPB. Table 2 shows temperature and hemodynamic comparisons between the two groups at the same time that blood samples were drawn. No significant differences in temperature, systolic blood pressure, diastolic blood pressure, or heart rate were observed in the two groups.

Plasma  $\beta$ -endorphin IR, quantitated in pg/ml as shown in Table 3, was significantly higher in the halothane group than in the fentanyl group as the patients were leaving the operating room ( $P < 0.01$ ), but no difference in absolute values was seen either preoperatively or intraoperatively. To account for patient-to-patient variability, we looked at the percentage of change in plasma  $\beta$ -endorphin IR in each patient as compared to his baseline. These results are plotted in Figure 1. After accounting for patient variability, plasma  $\beta$ -endorphin IR is seen to be significantly increased in the halothane group at rewarming on CPB and at leaving the operating room ( $P < 0.01$ ). No patients in either the halothane group or the fentanyl group reported any intraoperative awareness.

## Discussion

The radioimmunoassay employed in this study recognizes  $\beta$ -lipotropin with as much as 50% cross-reactivity. Because  $\beta$ -lipotropin and  $\beta$ -endorphin share

Table 1. Group Comparisons

	Fentanyl group ( <i>n</i> = 9)	Halothane group ( <i>n</i> = 6)
Age (yr)	54.0 $\pm$ 2.5	61.0 $\pm$ 2.3
Weight (kg)	85.3 $\pm$ 5.5	77.5 $\pm$ 5.5
Height (cm)	179.2 $\pm$ 2.8	177.5 $\pm$ 2.7
Pump prime (L)	1.71 $\pm$ 0.07	1.67 $\pm$ 0.10
Pump flow (L/min)	3.06 $\pm$ 0.13	3.08 $\pm$ 0.10
Diazepam (mg)	16.7 $\pm$ 2.1	20.0 $\pm$ 4.1
Anesthetic time (min)	286 $\pm$ 5	269 $\pm$ 2
Bypass time (min)	88 $\pm$ 5	76 $\pm$ 10

Values are means  $\pm$  SEM.

the same molecular precursor, plasma  $\beta$ -endorphin IR serves as an index of the stress response as mediated by the anterior pituitary. Our results agree with those of Dubois et al. (4), in that plasma  $\beta$ -endorphin IR was not elevated after induction of anesthesia. However, Dubois found elevated  $\beta$ -endorphin IR resulting from surgical stress alone, and our results showed no elevation in  $\beta$ -endorphin IR after incision. The reason for this is the difference in depth of anesthesia when the skin incision was made. Dubois' patients underwent a thiopental/succinylcholine induction for laparotomy; whereas, our patients had induction with fentanyl or halothane for coronary artery bypass surgery.

Roizen et al. have shown that stress response to surgical incision as measured by norepinephrine is a dose-related phenomenon for enflurane, halothane, and morphine (15). However, halothane has a dose-related depressant effect on the myocardium (16), and so a trade-off emerges between attenuation of the stress response and depression of the cardiovascular system. The dose of halothane needed to block the stress response may not be tolerated by the heart after termination of CPB. As a result, patients tend to be run at a lighter level of anesthesia after bypass when halothane alone is used.

Because  $\beta$ -endorphin,  $\beta$ -lipotropin, and ACTH share the same molecular precursor, it is not surprising to see  $\beta$ -endorphin IR as much a part of the stress response as ACTH. However, at this stage we can only speculate on what  $\beta$ -endorphin and  $\beta$ -lipotropin represent as part of that stress response. The analgesic properties of  $\beta$ -endorphin are well known, but its existence in the plasma at times of stress implies some other stress-related hormone-like function.

In their study of the use of halothane anesthesia for cardiac surgery, Wilkinson et al. (17) concluded that myocardial ischemia during halothane anesthesia did not appear to be directly related to the hemodynamic changes induced. They went on to implicate an as yet undiscovered factor involved in the use of

Table 2. Temperature and Hemodynamic Comparisons

	Baseline	Induction	Intubation	Incision	Rewarming	Leaving OR
Temperature ( $^{\circ}\text{C}$ )						
Halothane	—	$34.7 \pm 0.0$	$35.1 \pm 0.4$	$35.0 \pm 0.3$	$30.4 \pm 0.9$	$34.9 \pm 0.4$
Fentanyl	$36.0 \pm 0.0$	$35.7 \pm 0.7$	$35.6 \pm 0.2$	$35.3 \pm 0.4$	$31.2 \pm 0.7$	$35.4 \pm 0.2$
Systolic BP (torr)						
Halothane	$143 \pm 11$	$102 \pm 6$	$108 \pm 8$	$119 \pm 10$	$59 \pm 6$	$110 \pm 6$
Fentanyl	$134 \pm 11$	$112 \pm 4$	$112 \pm 7$	$126 \pm 8$	$61 \pm 3$	$124 \pm 6$
Diastolic BP (torr)						
Halothane	$74 \pm 6$	$66 \pm 6$	$65 \pm 4$	$77 \pm 6$	$59 \pm 6$	$71 \pm 4$
Fentanyl	$72 \pm 5$	$66 \pm 3$	$72 \pm 5$	$76 \pm 4$	$61 \pm 3$	$77 \pm 5$
Heart rate ( $\text{min}^{-1}$ )						
Halothane	$53 \pm 5$	$56 \pm 4$	$55 \pm 4$	$60 \pm 13$	—	$71 \pm 6$
Fentanyl	$69 \pm 6$	$65 \pm 3$	$64 \pm 4$	$60 \pm 4$	—	$88 \pm 6$

Values are means  $\pm$  SEM.Table 3. Plasma  $\beta$ -Endorphin Immunoreactivity (pg/ml)

	Baseline	Induction	Intubation	Incision	Rewarming	Leaving OR
Halothane	$26.2 \pm 7.6$	$27.0 \pm 8.0$	$19.3 \pm 9.1$	$25.1 \pm 4.9$	$31.9 \pm 12.0$	$70.5 \pm 9.1^a$
Fentanyl	$21.4 \pm 4.3$	$20.4 \pm 4.6$	$17.6 \pm 2.4$	$23.2 \pm 3.7$	$16.2 \pm 5.2$	$20.0 \pm 3.6$

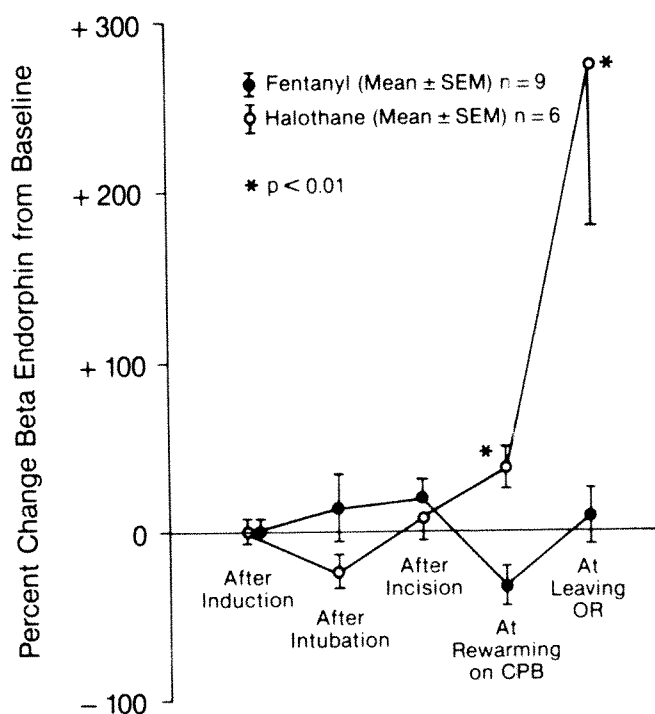
<sup>a</sup> $P < 0.01$  between groups.

Figure 1. Percent change in plasma  $\beta$ -endorphin IR for each patient as compared to preoperative baseline is significantly greater in the halothane group than in the fentanyl group during cardiopulmonary bypass and upon leaving the operating room ( $P < 0.01$ ).

halothane as a source of the observed ischemia. Is it possible that the effects of stress hormones contribute to myocardial ischemia? Wilkinson et al. speculated that intraoperative stress-induced vasospasm may well

override the increased myocardial metabolic demand as a cause of myocardial ischemia (18). Obviously, the final answer is not available on the significance or risk of stress during anesthesia, but these observations on myocardial ischemia are intriguing, and, with the information available, we believe it is better to avoid stress than not.

In conclusion, this study showed that plasma  $\beta$ -endorphin IR was well controlled prior to CPB in both the halothane group and fentanyl group. This control was extended throughout the study time for the fentanyl group. The halothane group showed a marked stress response, as measured by plasma  $\beta$ -endorphin IR, during cardiopulmonary bypass, when the halothane was discontinued. The halothane group also demonstrated a stress response after cardiopulmonary bypass, when halothane was administered only to the extent that it did not cause cardiac depression. Thus the halothane group was not as well protected from the stress response as was the fentanyl group.

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## The Hemodynamic Consequences of High-Dose Thiopental Anesthesia

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TODD MM, DRUMMOND JC, U HS. The hemodynamic consequences of high-dose thiopental anesthesia. *Anesth Anal* 1985;64:681-7.

*The hemodynamic and electroencephalographic effects of a 60 min infusion of thiopental, given at the rate of  $1.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (total dose 75 mg/kg), were studied in 10 patients without cardiorespiratory disease undergoing surgery for the removal of large and/or deeply seated arteriovenous malformations. Data on heart rate, arterial, right atrial, pulmonary arterial, and pulmonary capillary wedge pressures, thermodilution cardiac output (expressed as cardiac index), the electroencephalogram, arterial blood gases, and serum thiopental concentrations were collected during a sedated, resting control period, and then every 15 min during drug infusion. Lactated Ringer's solution (total volume 1-2 liters) was infused throughout the study period at rates sufficient to maintain pulmonary capillary wedge pressure at control values.*

*In doses sufficient to render the electroencephalogram isoelectric [ $t \approx 30 \text{ min}$ ,  $37.5 \text{ mg/kg}$  cumulative dose, serum concentration  $51 \pm 17 \text{ } \mu\text{g/ml}$  (mean  $\pm$  SD)], drug infusion resulted in significant increases in heart rate (to 116% of control), and decreases in arterial pressure (to 87% of control), stroke volume index (to 87% of control), sys-*

*temic resistance (84% of control), and both left and right ventricular stroke work indices (66% and 69% of control, respectively). Cardiac index was unchanged (following a transient increase at  $t = 15 \text{ min}$ ). There were no changes in pulmonary capillary wedge pressure, pulmonary arterial, pulmonary vascular resistance, or blood gases. A large total dose of thiopental (8-11 gm) was needed to maintain electroencephalogram suppression for the remainder of these 10-20 hr procedures, and emergence was slow (48-72 hr). The resultant prolonged ICU support may have contributed to serious postoperative complications in two patients.*

*These results demonstrate that high concentrations of thiopental are associated with vasodilation and myocardial depression, changes which were similar to those seen in a previous study using methohexital. However, they were of a lesser magnitude than reported with electroencephalographically equivalent doses (2.0 MAC) of isoflurane, suggesting that barbiturates may be hemodynamically preferable if profound electroencephalogram suppression is desired. However, their use is not without risk, and such an anesthetic should be undertaken only with the utmost caution.*

**Key Words:** ANESTHESIA—neurosurgical. ANESTHETICS, INTRAVENOUS—thiopental, methohexital.

There have been many studies of the hemodynamic effects of thiopental in humans (1-10), but most have examined changes occurring after the bolus injection of "standard" induction doses, i.e., 3-6 mg/kg. There is little information concerning the effects of much larger amounts of the drug in humans (11,12). Since high-dose barbiturate anesthesia has recently achieved a limited measure of popularity in neurosurgery (12), such information is needed.

Recently, we reported on the hemodynamic effects of a high-dose methohexital infusion (24 mg/kg over 1 hr) performed in eight neurosurgical patients (13).

However, the occurrence of seizures in three of the patients after discontinuing the drug led us to abandon its use. Therefore we chose to complete an examination of the effects of thiopental that had been started earlier (14). This report presents the hemodynamic and electroencephalographic changes that accompanied the infusion of very large doses of thiopental (75 mg/kg over 60 min) in humans. In addition to providing information concerning the effects of thiopental, the similarity in design between this project and our work with methohexital permits comparisons between the effects of these two anesthetic barbiturates.

### Materials and Methods

Ten neurosurgical patients ranging in age from 12 to 42 yr were studied. All were undergoing surgery for the staged removal of large and/or deeply seated arteriovenous malformations (AVMs). Five of the pa-

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tients had previously received a methohexital anesthetic during a previous operation (and were included in the previous report), but none had received anesthetic doses of barbiturates within three months prior to the current study. One other patient received thiopental, but technical difficulties prevented complete data collection, and two other individuals received a different dosage of drug and are not included here.<sup>1</sup> Except for their neurosurgical disorders, they were free of other disease. All were taking either prophylactic or therapeutic anticonvulsants, and all were alert and intellectually intact. In each case, a high-dose barbiturate anesthetic was selected in an attempt to minimize problems associated with the so called "reperfusion-breakthrough syndrome" (13,15-17), and was administered with the full and detailed informed consent of the patients (or parents). Separate informed consent was obtained for the hemodynamic measurements and blood samples used in these investigations. The studies were approved by the Human Experimentation Committee of the University of California, San Diego School of Medicine.

The study protocol was essentially identical to that described in our previous report on methohexital (13). Premedication consisted of oral lorazepam 2-4 mg the night before surgery, and oral diazepam 5-15 mg in the early morning. Morphine 2-5 mg and diazepam 5-7.5 mg were given intravenously in the operating room. All the patients were sleepy on arrival in the operating room, but were responsive to conversation and command. They were placed on the operating table with the head and torso approximately 5° above the horizontal (table flexed, legs flat). Monitored vascular variables included heart rate (HR); arterial pressure (BP); right atrial (RAP), pulmonary arterial (PAP) and pulmonary capillary wedge pressures (PCWP); and thermodilution cardiac output measured in triplicate (using an Edwards 9520A computer and a 7 or 7.5 F thermistor-tipped Swan-Ganz catheter). All pressures were referenced to the level of the right atrium, were recorded at end-expiration, and are expressed as electrical means. The ECG was also monitored along with a 2-channel electroencephalogram (EEG-bipolar leads FP<sub>1</sub>-O<sub>1</sub>, FP<sub>2</sub>-O<sub>2</sub>, using platinum subdermal electrodes). Expired CO<sub>2</sub> (initially sampled from the anesthesia mask and later from the proximal end of the endotracheal tube) was measured using an infrared analyzer (Beckman LB-II) or a mass spectrometer (Chemetron), while inspired oxygen con-

centration (FI<sub>O<sub>2</sub></sub>) was monitored using a polarographic instrument. Temperature was recorded in the pulmonary artery, using the pulmonary artery catheter thermistor and cardiac output computer.

After monitoring devices were in place, the patients were left undisturbed on the operating table for 10 min. An anesthesia mask was then placed on the face, and 50% oxygen (in air) was administered for an additional 10 min. Control data were obtained, and an infusion of sodium thiopental (25 mg/ml in water) was started at a rate of 1.25 mg·kg<sup>-1</sup>·min<sup>-1</sup>, using an IVAC 630 pump. This rate was not changed for the next 60 min (total dose over 1 hr, 75 mg/kg). Approximately 3 min after the start of drug infusion, a combination of pancuronium (0.03 mg/kg) and metocurine (0.12 mg/kg) (18) was administered and manual ventilation begun. A nasopharyngeal airway was placed if necessary. FI<sub>O<sub>2</sub></sub> was kept at 0.50, while end-tidal expired CO<sub>2</sub> was maintained between 4.0 and 4.5% by varying respiratory rate. Care was taken to avoid increases in end-expiratory airway pressure, and temperature was maintained at 36-37°C using warming blankets, fluid warmers, and a heated humidifier. The EEG was recorded continuously.

The thiopental infusion was continued at the described rate for 60 min, with hemodynamic variables recorded at 15 min intervals. Throughout the experimental period (0-60 min after the start of drug infusion), lactated Ringer's solution was infused at a rate sufficient to maintain PCWP at control values (see Discussion). Immediately after recording data at  $t = 45$  min (i.e., 12-13 min before the  $t = 60$  min data point) a nasotracheal tube was placed. Except for this and the placement of the nasopharyngeal airway, no other stimulus was permitted during the 60-min induction period. After data collection at  $t = 60$  min, the thiopental infusion rate was reduced to approximately 0.25 mg·kg<sup>-1</sup>·min<sup>-1</sup>, and was thereafter titrated to maintain either EEG isoelectricity or deep burst suppression (minimum infusion rate, 0.05 mg·kg<sup>-1</sup>·min<sup>-1</sup>). However, because of widely differing surgical circumstances (patient position, the use of hypothermia or induced hypotension, or both), systematic data collection was not carried out beyond the induction period.

In eight of the patients, arterial samples for the determination of serum thiopental concentration were drawn 0, 15, 30, 45 and 60 min after the start of drug infusion. Drug concentrations were measured using high performance liquid chromatography and are expressed as µg/ml (19). Samples for the determination of PaO<sub>2</sub>, PaCO<sub>2</sub>, pH<sub>a</sub>, and hematocrit (Hct) were also obtained at similar intervals (all patients). Calculated variables (obtained using standard formulas) were

<sup>1</sup>The results in the first five of the present patients were previously published in abstract form (see ref. 14). Four of these patients are included in the current report; data from one were discarded because of a subsequently discovered dosage error.

Table 1. Data Summary

	Control	15 min	30 min	45 min	60 min
Heart rate (beats/min)	82 ± 18	97 ± 24 <sup>a</sup>	96 ± 25 <sup>a</sup>	93 ± 24 <sup>a</sup>	94 ± 24 <sup>a</sup>
BP (mm Hg)	85 ± 11	75 ± 13 <sup>a</sup>	73 ± 12 <sup>a</sup>	70 ± 9 <sup>a</sup>	71 ± 11 <sup>a</sup>
RAP (mm Hg)	5 ± 3	5 ± 3	5 ± 2	5 ± 3	6 ± 2
PAP (mm Hg)	14 ± 6	14 ± 5	14 ± 5	14 ± 5	14 ± 5
PCWP (mm Hg)	8 ± 4	9 ± 4	9 ± 4	9 ± 5	9 ± 5
CI (L·min <sup>-1</sup> ·m <sup>-2</sup> )	4.0 ± 0.4	4.4 ± 0.7 <sup>a</sup>	4.1 ± 0.8	3.9 ± 0.8	3.7 ± 1.0
SVI (ml·beat <sup>-1</sup> ·m <sup>-2</sup> )	50.2 ± 12.0	46.5 ± 18.9	43.7 ± 8.7 <sup>a</sup>	43.1 ± 10.9 <sup>a</sup>	41.2 ± 11.2 <sup>a</sup>
SVRI (mm Hg·L <sup>-1</sup> ·min·m <sup>-2</sup> )	20.6 ± 3.7	16.3 ± 3.3 <sup>a</sup>	17.3 ± 3.6 <sup>a</sup>	17.3 ± 3.4 <sup>a</sup>	18.2 ± 3.8
PVRI (mm Hg·L <sup>-1</sup> ·min·m <sup>-2</sup> )	1.7 ± 0.9	1.5 ± 0.8	1.6 ± 1.0	1.6 ± 1.2	1.7 ± 1.3
LVS WI (mm Hg·ml·beat <sup>-1</sup> ·m <sup>-2</sup> )	3867 ± 1148	3151 ± 1042 <sup>a</sup>	2848 ± 779 <sup>a</sup>	2628 ± 811 <sup>a</sup>	2571 ± 831 <sup>a</sup>
RVS WI (mm Hg·ml·beat <sup>-1</sup> ·m <sup>-2</sup> )	508 ± 322	453 ± 157 <sup>a</sup>	408 ± 185 <sup>a</sup>	376 ± 177 <sup>a</sup>	349 ± 181 <sup>a</sup>
PaO <sub>2</sub> (mm Hg)	228 ± 32	229 ± 40	218 ± 44	223 ± 56	218 ± 57
Paco <sub>2</sub> (mm Hg)	40 ± 5	43 ± 6	43 ± 9	44 ± 7	39 ± 6
pH	7.38 ± 0.02	7.37 ± 0.05	7.37 ± 0.07	7.36 ± 0.06	7.41 ± 0.08
Hgb (gm/dl)	13.1 ± 2.2	12.6 ± 2.6	12.4 ± 2.6 <sup>a</sup>	12.5 ± 2.2 <sup>a</sup>	12.6 ± 2.2 <sup>a</sup>

All values are mean ± SD.

<sup>a</sup>*P* < 0.05 vs control.

Abbreviations: HR, heart rate; BP, mean arterial pressure; RAP, mean right atrial pressure; PAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVI, stroke volume index; SVRI and PVRI, systemic (S) and pulmonary (P) vascular resistance index; LVS WI and RVS WI, left (L) and right (R) ventricular stroke work index; Hgb, hemoglobin concentration.

expressed as indices (per m<sup>2</sup>) and included cardiac index (CI, L·min<sup>-1</sup>·m<sup>-2</sup>), stroke volume index (SVI, ml·beat<sup>-1</sup>·m<sup>-2</sup>), systemic and pulmonary vascular resistance indices (SVRI and PVRI, mm Hg·L<sup>-1</sup>·min<sup>-1</sup>·m<sup>-2</sup>), and both left and right ventricular stroke work indices (LVS WI and RVS WI, mm Hg·ml<sup>-1</sup>·beat<sup>-1</sup>·min<sup>-1</sup>·m<sup>-2</sup>).

Statistical analysis was performed using an analysis of variance for repeated measures, followed, where indicated, by paired *t*-tests with Bonferroni corrections. All data are reported as mean ± SD, and significance was assumed for *P* < 0.05.

## Results

Technically adequate EEGs were obtained in eight of the patients. Drug infusion produced the well-described characteristic sequence of changes expected for the barbiturates (3,20), with initial periods of suppression (lasting <1 sec) appearing at 8 ± 3 min (mean ± SD) after the start of the infusion. Typical "burst-suppression" patterns (8–12 burst per min) appeared at 14 ± 4 min, while isoelectricity (no detectable activity for greater than 2 min at a 5 μV/mm gain) was noted at 22 ± 7 min.

Serum thiopental concentrations (obtained in eight patients) increased progressively to 35 ± 13, 51 ± 17, 66 ± 25, and 75 ± 36 μg/ml at 15, 30, 45, and 60 min respectively (*n* = 8).

Other measured values are summarized in Table 1. Since PCWP was controlled (by the infusion of 1–2 liters of fluid), no changes were expected and none were noted. There were also no changes in RAP. HR

increased significantly at 15 min (97 ± 24 beats per min or 117% of control) and remained elevated thereafter. CI increased transiently at 15 min (4.4 ± 0.7 L·min<sup>-1</sup>·m<sup>-2</sup>, or 110% of control), returning to values statistically indistinguishable from control at 30 min and thereafter. As a result, calculated SVI decreased progressively, with significance achieved at 30 min, reaching a value of 41.2 ± 11.2 ml·beat<sup>-1</sup>·m<sup>-2</sup> (82% of control) at 60 min. BP decreased from 84.5 ± 10.7 mm Hg in the control period, to a minimum of 70.0 ± 8.8 mm at *t* = 45 min, remaining at 71.0 ± 11.3 mm Hg at *t* = 60 min. Calculated SVRI reached a minimum of 16.3 ± 3.3 mm Hg·L<sup>-1</sup>·min<sup>-1</sup>·m<sup>-2</sup> at *t* = 15 min, increasing thereafter, with the recorded value of SVRI at *t* = 60 min not being significantly different from control. There were no changes in PVRI at any time.

Both LVS WI and RVS WI decreased progressively, reaching values of 66% and 69% of control at *t* = 60 min. There were no changes in PaO<sub>2</sub>, Paco<sub>2</sub>, or pH. Since a maximum of 60 ml of blood was drawn in a given patient, the small reduction in hemoglobin concentration was presumably the result of dilution due to the volume of infused fluid needed to maintain PCWP.

## Discussion

The protocol described was designed to permit an examination of the cardiovascular effects of very large doses of thiopental under optimally controlled conditions, i.e., hemodynamically normal patients, a resting (unstressed) control state, gradually increas-



ing blood concentrations of the drug (no bolus effect), no other anesthetic agents (specifically, no  $N_2O$ ), controlled ventilation, EEG monitoring, and an absence of surgical stimuli. In addition, constant left ventricular filling pressures (as an approximation of preload) were maintained in an attempt to avoid at least some of the confusion that arises when attempting to interpret hemodynamic values recorded in the face of simultaneously changing preload, afterload, and intrinsic contractility. The only factors that might have served to complicate these observations were the stimulus associated with endotracheal intubation; the slight head-up posture employed; and the possibility that the neurovascular lesions in these patients might have somehow altered their responses. The last factor is impossible to rule out, although control values were normal and the responses to drug infusion were qualitatively similar to those described by others (see below). The chosen position should be unimportant because "venous pooling" was offset by fluid infusion, and lastly, intubation was completed at least 12-13 min before the final data collection point. Therefore, the experimental circumstances were nearly optimum for carefully evaluating the *in vivo* responses to these doses of thiopental.

Our results qualitatively mirror those of other investigators. For example, the requirement for 1-2 liters of intravenous fluid to maintain PCWP during drug infusion indirectly indicates some degree of venodilation, an observation supported by the earlier work of Eckstein et al. (5), Etsen and Li (2), and by Flickinger et al. (6), as well as by Reiz et al. (10). This was also accompanied by arterial vasodilation, as evidenced by a significant (although transient) reduction in SVRI. This has been reported with lower drug doses (4,10), although it has been an inconsistent finding (3,6). Lastly, most previous workers have noted barbiturate-mediated decreases in stroke volume (2-4,6,7,9,10) with accompanying (but not necessarily compensatory (13,21)) increases in HR, although with variable net effects on CI. These data combine to demonstrate that thiopental is both a vasodilator and a myocardial depressant. The depressant effects of thiopental we observed *in vivo* have also been reported in *in vitro* studies (22,23), and one group has shown that at least one barbiturate (pentobarbital) is an *in vitro* vasodilator (24).

While the aforementioned summary of qualitative changes is of interest, the quantitative effects of the large doses are more important. In amounts sufficient to render the EEG isoelectric (after approximately 30 min, blood concentration  $51 \pm 17 \mu g/ml$ ), the changes in most measured variables were surprisingly modest. The CI was unchanged, HR increased by  $13 \pm 16$

beats/min above baseline (to  $117 \pm 18\%$  of control), BP decreased by  $11 \pm 13$  mm Hg (to a value 87% of control), while SVI decreased to  $88 \pm 11\%$  of control, and SVRI was reduced to  $85 \pm 14\%$  of baseline. By comparison, Sonntag et al. (7) examined the changes occurring after a 4 mg/kg bolus dose of thiopental (measurements made approximately 2 min after injection), and noted that cardiac output decreased to 84% of control, HR increased by 26 beats/min (to 132% of control), BP decreased 7 mm Hg (to 93% of control), and SVI decreased  $17 \text{ ml} \cdot \text{beat}^{-1} \cdot \text{m}^{-2}$  (to 65% of baseline). PCWP was not changed. Even the larger doses (e.g., 15 mg/kg) given by Koht et al. did not result in changes appreciably different from those seen in our patients (11). This indicates that even very large doses of thiopental, when given in the manner described, do not produce hemodynamic changes substantially different from those seen with "standard" induction doses of the drug. This may be the result of the slowly rising blood concentrations, which may, in turn, permit various compensatory mechanisms to come into play.

One further comparison serves to place in perspective the changes seen in this study. Recently, isoflurane has been proposed as a cerebral protective agent, similar to the barbiturates, based on its demonstrated effects on the EEG, cerebral blood flow, and metabolism, etc. (25). Newberg et al. noted that isoflurane prolongs hypoxic survival in mice, and that concentrations sufficient to render the EEG isoelectric (e.g., approximately 2.0 MAC) minimize changes in cerebral high energy phosphates and lactate during profound hemorrhagic hypotension in the dog (26). They also noted that isoflurane-induced hypotension to 30 mm Hg was not associated with evidence of serious energy failure; in contrast to hypotension produced by halothane (27). Finally, Lam and Gelb have used isoflurane in approximately 2 MAC concentrations for the induction of hypotension during neurovascular surgery (28). It is therefore of interest to review the hemodynamic effects of 2.0 MAC isoflurane (in  $O_2$ ) as described by Stevens et al. in mechanically ventilated, normocapnic, unstimulated human volunteers (29). They noted that cardiac output was statistically unchanged (89% of control vs 103% for thiopental in the current study), HR increased to 120% of control, while BP and SVR decreased to values of 46% and 49% of control, respectively. Stroke volume decreased to  $75 \pm 4\%$  of control. PCWP was not recorded, but RAP increased by 1.5 mm Hg, and LVSWI decreased to 44% of control (vs 74% for thiopental). These data suggest (although they cannot be taken as proof) that isoflurane in doses "equivalent" to thiopental in terms of EEG suppression, may have

a greater impact on hemodynamic performance than do the barbiturates, at least in terms of BP, SVR, and myocardial function. Furthermore, even much larger thiopental doses, such as those at  $t = 45$  and  $60$  min, were not associated with as great a reduction in BP, SVR, or LVSWI as was 2 MAC isoflurane. The implication is that the barbiturates may be hemodynamically preferable to isoflurane in situations when profound depression of the EEG and cerebral metabolism is desired.

One final comparison is worthwhile. The protocol used for the current study was identical to that used in our earlier work with methohexital (13); and, while the infusion rates for the two studies were intended to be only roughly equivalent ( $0.4 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  of methohexital vs  $1.25 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  of thiopental), examination of the various of EEG end-points suggests that the doses were, in fact, approximately equipotent, i.e., EEG isoelectricity occurred at  $28 \pm 13$  min with methohexital vs  $22 \pm 7$  min for thiopental (difference not significant by unpaired  $t$ -testing). The hemodynamic changes observed with both drugs at 30 min are shown in Table 2, and it is apparent that their effects are almost indistinguishable, at least within the limitations imposed by the study protocol. Comparable similarities can be seen at even larger doses. This conclusion is similar to that drawn by Dobkin and Wyant (4), by Conway et al. (30), and by Conway and Ellis (31), all using lower drug doses. This conclusion is also supported by the studies of Boarini et al. who examined high dose thiopental and methohexital anesthesia in dogs (32). It should be noted that our work provides no data on the comparable cerebral effects of thiopental and methohexital (beyond the EEG), but Boarini et al. noted that both produce comparable reductions in cerebral blood flow and cerebral metabolic rate for oxygen ( $\text{CMRO}_2$ ) when given in doses sufficient to yield comparable degrees of EEG suppression (32).

The above discussions have focused on the initial 60 min of anesthesia in our patients. However, additional clinical comments are in order. All patients survived their surgical procedures, and the only new neurologic deficit noted was a mild left hemiparesis in one patient who underwent partial resection of a lesion in the right basal ganglia. The other patients all returned to their baseline neurologic status, and there were no significant intraoperative complications in any of the patients. The total dose of thiopental ranged from 8–11 g over 10–20 hr of surgery, and all patients remained asleep for 48–72 hr after discontinuation of the drug administration. The postoperative courses were otherwise uneventful in eight of the ten patients. However, one patient developed a severe

Table 2. Thiopental vs Methohexital

	Thiopental		Methohexital	
HR	$96 \pm 25$	(116)	$102 \pm 15$	(131)
BP	$73 \pm 12$	(87)	$70 \pm 12$	(84)
CI	$4.1 \pm 0.8$	(103)	$4.4 \pm 0.8$	(113)
SVI	$43.7 \pm 8.7$	(87)	$43.6 \pm 10.4$	(87)
SVRI	$17.3 \pm 3.6$	(84)	$15.4 \pm 3.9$	(73)
LVSWI	$2848 \pm 779$	(74)	$2628 \pm 543$	(71)
PaO <sub>2</sub>	$218 \pm 44$		$214 \pm 33$	
Serum concentration ( $\mu\text{g/ml}$ )	$51 \pm 17$		$12 \pm 3$	

Selected hemodynamic values at  $t = 30$  min after the initiation of an infusion of thiopental ( $1.25 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , this study) or methohexital ( $0.4 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , see ref. 13). See Table 1 for abbreviations. Values are mean  $\pm$  SD, and the numbers in parentheses are percent of control. There were no differences in control values between the two studies (unpaired  $t$ -test), nor were there any statistical differences in the values shown above. Note, however, that statistical comparisons between the studies must be interpreted with caution because, although the infusion rates were roughly equivalent, no attempt was made to use exactly equivalent doses.

bacterial pneumonia and respiratory failure beginning approximately 48 hr postoperatively, necessitating mechanical ventilation with PEEP for an additional seven days. A second patient (a 21-yr-old athlete) developed a hyperdynamic cardiovascular picture 24 hr postoperatively ( $\text{CI} > 13 \text{ L/min}$ ,  $\text{BP} > 160$  systolic,  $\text{HR} > 130$  beats/min) requiring aggressive antihypertensive therapy and ICU support. This same individual also suffered a postoperative subarachnoid hemorrhage secondary to his hypertension, and a pseudomonas ventriculitis requiring intraventricular antibiotics. Fortunately, in spite of his difficult course, he was discharged neurologically intact one month after surgery. These last two cases, however, point out a potential danger associated with large doses of thiopental, because it is possible that neither event would have occurred in the absence of prolonged postoperative sedation. This persistent drug effect presumably reflects the altered pharmacokinetic picture described by Stanski et al., where persistent plasma concentrations higher than  $60 \mu\text{g/ml}$  (sufficient to suppress EEG activity, as in our study) result in saturation of metabolizing enzymes, a change to zero-order kinetics, and an eliminated half-life that may exceed 60 hr (33). This is in marked contrast to the first order kinetics and elimination  $t_{1/2}$  of 10–12 hr noted after traditional surgical doses (34). In contrast to our experiences with methohexital (13), there were no postoperative seizures.

In summary, our experiences with thiopental (and with methohexital) indicate that very large doses of these drugs can be administered with minimal hemodynamic risk, at least when the described guidelines are followed, i.e., young, cardiovascularly normal pa-

tients, gradual drug infusion rather than bolus injection, monitored and controlled PCWP, etc. When such constraints are observed, plasma thiopental concentrations sufficient to render the EEG isoelectric were associated with an unchanged CI, 13% reductions in BP and SVI, and a 26% decrease in LVSWI. However, the reductions in the last three parameters were less than reported for an electroencephalographically equivalent dose of isoflurane, perhaps suggesting an advantage to the use of barbiturates if profound EEG suppression is a desired goal (e.g., for ischemic protection). Nevertheless, the hemodynamic feasibility of high-dose barbiturate anesthesia does not imply that such a use is clinically efficacious (in terms of outcome), nor does it rule out other "nonhemodynamic" drawbacks, such as the withdrawal seizures noted previously with methohexital, or the prolonged emergence and ICU complications seen here. Efforts are underway to minimize these difficulties by using various barbiturate combinations along with adjuvant agents. However, until these experiments are complete, and until actual benefits of barbiturates can be confirmed in humans (as opposed to animals), it is crucial that such anesthetic techniques be undertaken only with great care, and only when the indications and problems are understood by all concerned.

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## A Comparison of the Sensitivity of Pulmonary Artery Pressure, End-Tidal Carbon Dioxide, and End-Tidal Nitrogen in the Detection of Venous Air Embolism in the Dog

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- DRUMMOND JC, PRUTOW RJ, SCHELLER MS. A comparison of the sensitivity of pulmonary artery pressure, end-tidal carbon dioxide, and end-tidal nitrogen in the detection of venous air embolism in the dog. *Anesth Analg* 1985;64:688-92.

*The authors sought to define the relative sensitivities of end-tidal carbon dioxide analysis (ETCO<sub>2</sub>), end-tidal nitrogen analysis (ETN<sub>2</sub>), and pulmonary artery pressure (PAP) monitoring in the detection of venous air embolism (VAE). Serial injections of air (0.25, 0.5, 0.75, 1.0, and 1.5 ml/kg) were performed in six mongrel dogs. The frequency with which positive responses (PAP increase > 2 mm Hg; ETCO<sub>2</sub> decrease > 0.2%; ETN<sub>2</sub> increase > 0.04%) were observed following VAE was not different for the three methods. The response time (time to maximum change following VAE) was significantly more rapid for PAP and ETN<sub>2</sub> than for ETCO<sub>2</sub>; although the range for the three methods was narrow, e.g., for 1.5 ml/kg—PAP, 0.92 ± 0.7 (SD) min; ETN<sub>2</sub>, 1.20 ± 0.5 min; ETCO<sub>2</sub>, 1.85 ± 0.7 min. The time from injection of air to return to baseline levels was significantly*

*more rapid for ETN<sub>2</sub> than for ETCO<sub>2</sub> which was in turn significantly faster than PAP, e.g., for 1.5 ml/kg—ETN<sub>2</sub>, 8.0 ± 4.3 min; ETCO<sub>2</sub>, 19.4 ± 6.0 min; PAP, 23.8 ± 6.1 min. The results indicate that, where the capacity to identify increases in expired nitrogen on the order of 0.04% can be achieved, ETN<sub>2</sub> monitoring will identify VAE events with a sensitivity similar to that of PAP and ETCO<sub>2</sub>. However, the difficulties inherent in achieving this level of nitrogen detection sensitivity probably represent a current major limitation in the application of this method. Furthermore, the data indicate that, after VAE, ETN<sub>2</sub> will return to preinjection levels although PAP and ETCO<sub>2</sub> remain abnormal. This observation suggests that ETN<sub>2</sub> may not be a reliable indicator of recovery from the physiologic impact of VAE, and may therefore not be the optimum method to base decisions regarding resumption of the head-up posture and continuation of surgery during procedures in which VAE has occurred.*

**Key Words:** EMBOLISM—air. MONITORING—end-tidal gases.

It has been demonstrated in oxygen-breathing animals that the injection of air into the venous circulation is followed promptly by the appearance of nitrogen in the expired gas (1). Monitoring of expired nitrogen has therefore been proposed as another means for the detection of intraoperative venous air embolism (VAE). End-tidal nitrogen (ETN<sub>2</sub>) analysis has the theoretical advantage that, in the absence of any variation in inspired nitrogen concentration, it should be

both specific and quantitative. However, its ultimate usefulness will be determined by its sensitivity relative to that of the other available VAE monitoring methods. There is at present a wide gulf between the highly sensitive precordial Doppler (2) and the next echelon of VAE detection sensitivity, i.e., monitoring of end-tidal carbon dioxide (ETCO<sub>2</sub>) and pulmonary artery pressure (PAP) (3,4). These latter two methods have the advantage of providing quantitative information about VAE, but they have a detection threshold markedly higher than that of the precordial Doppler (4). A technique that would provide a level of sensitivity greater than ETCO<sub>2</sub> and PAP, and at the same time provide quantitative information would have considerable appeal. We undertook the present study to define the sensitivity of ETN<sub>2</sub> relative to that of PAP and ETCO<sub>2</sub>. This study is similar in general format to an earlier investigation by English et al. (4). That work provided an important and comprehensive comparison of the sensitivities of the then-available VAE de-

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tection methods that included PAP and  $\text{ETCO}_2$ , but not  $\text{ETN}_2$ .

## Methods

The protocol was approved by the Animal Research Committee of the University of California, San Diego. Anesthesia was induced in six mongrel dogs (weight  $\pm$  SD,  $25.7 \pm 8.1$  kg) with pentobarbital, 40 mg/kg intravenously, and maintained with increments of pentobarbital totaling approximately  $100 \text{ mg}\cdot\text{hr}^{-1}$ . The animals were intubated and mechanically ventilated with a tidal volume of approximately 17.5 ml/kg. The respiratory rate was adjusted to between 18 and 22 breaths per minute to maintain  $\text{PaCO}_2$  less than 35 mm Hg. To preclude contamination by atmospheric nitrogen, the ventilator (a Harvard Model 607 Respiration Pump) and the anesthetic circuit were sealed and pressure tested to 40 mm Hg prior to each study. The inspired gas was 100% medical grade oxygen delivered from a G cylinder in the experimental suite (i.e., a bulk  $\text{O}_2$  supply was not employed). The supplier (GS Parsons Co.) stated that the oxygen contained a nitrogen contaminant of approximately 0.04%. Independent analysis (by the laboratory of John B. West, UCSD) of the contents of a single G cylinder confirmed the accuracy of this statement.

The animals were positioned with the head and shoulders elevated  $30^\circ$ . Pulmonary arterial, abdominal aortic, and right atrial catheters were placed via femoral vessels; and a 5-cm, 18-gauge Teflon catheter (Deseret Angiocath) was placed nonocclusively in the right external jugular vein. Rectal temperature was servocontrolled to  $37^\circ\text{C}$  using a warming blanket and infrared lamps, and lactated Ringer's solution was infused at  $6 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ .

Continuous pan-tidal measurement of carbon dioxide (Beckman LB-2) and nitrogen (Perkin-Elmer 1100 Medical Gas Analyzer mass spectrometer) concentrations were performed on samples drawn via small bore polyethylene catheters from the tip of the endotracheal tube. Expired nitrogen was measured by directly recording the output of the collecting plate at which nitrogen is detected (see below). The linearity of the system at concentrations less than 1.5% was confirmed using serial dilutions of a 1.5% nitrogen in oxygen standard (Linde); the same standard was used for calibration prior to each study. Because carbon dioxide is "seen" on the nitrogen collecting plate in proportion to its concentration,<sup>1</sup> the nitrogen reading

Table 1. Frequency of Positive Responses (%) for End-Tidal  $\text{CO}_2$  ( $\text{ETCO}_2$ ), End-Tidal  $\text{N}_2$  ( $\text{ETN}_2$ ), and Pulmonary Artery Pressure (PAP), after Serial Injections of Air at 30-Min Intervals<sup>a</sup>

Volume injected (ml/kg)	0.25	0.50	0.75	1.0	1.5
PAP (mm Hg)	16.7	33.3	66.7	100	100
$\text{ETCO}_2$ (%)	16.7	66.7	83.3	100	100
$\text{ETN}_2$ (%)	16.7	50	83.3	100	100

<sup>a</sup>The frequency of positive responses was not significantly different for the three methods at any injectate volume.

was corrected for changes due to carbon dioxide. The correction factor was determined by observing the output of the nitrogen collecting plate during sampling of 0–6% carbon dioxide in oxygen.

A 45-min stabilization period followed the completion of instrumentation. After stabilization, a series of five air injections was made at 30-min intervals. The volumes injected were 0.25, 0.5, 0.75, 1.0, and 1.5 ml/kg, and the sequence was varied systematically. In each instance the air was injected over a period of 2 sec at the hub of the external jugular catheter, which was flushed continuously with a pump-driven infusion of Ringer's lactate at  $6 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ .

On the basis of the observed stability of  $\text{ETN}_2$ ,  $\text{ETCO}_2$ , and PAP during steady-state conditions, it was decided that any acute change equal to or greater than 0.04%, 0.2%, or 2 mm Hg, respectively, could be attributed to the injection of air. Accordingly any change equal to or greater than these amounts was considered a "positive response." After each injection, the maximum increases in mean PAP and peak  $\text{ETN}_2$ , and the maximum decrease in peak  $\text{ETCO}_2$  were noted. In addition, the times required for each variable to achieve the maximum alteration and to return thereafter to a stable baseline were determined from the polygraph record. The statistical significance of differences in the various time intervals was determined by a repeated measures analysis of variance. Where differences were detected, paired comparisons were performed using Student's *t*-test for paired data with the Bonferroni correction for multiple comparisons. The frequency of positive responses by the three techniques at each injectate volume was compared using the Fisher exact test.

## Results

The 45-min stabilization period was sufficient in all instances to provide for stable expired nitrogen concentrations. Peak  $\text{ETN}_2$  prior to air injection was on the order of 0.01% above inspired levels. This amount is probably near the method's level of sensitivity and it must suffice to say that expired levels were low and

<sup>1</sup>Gases are ionized before entering the magnetic field of the mass spectrometer and the ionization of  $\text{CO}_2$  results in the formation of small concentrations of carbon monoxide which has the same mass number (28) as nitrogen. The two molecules therefore behave similarly in the magnetic field and reach the same collecting plate.

Table 2. End-Tidal Carbon Dioxide (ETCO<sub>2</sub>) (%), End-Tidal Nitrogen (ETN<sub>2</sub>) (%), Mean Pulmonary Artery Pressure (PAP) (mm Hg), and Mean Arterial Pressure (MAP) (mm Hg), before (Pre) and after (Post) Injection of 1.0 and 1.5 ml/kg of Air<sup>a</sup>

Injectate	1.0 ml/kg			1.5 ml/kg		
	Pre	Post <sup>b</sup>	Δ	Pre	Post <sup>b</sup>	Δ
ETCO <sub>2</sub>	4.13 ± 0.7	3.37 ± 0.5	- 0.76 ± .29	3.88 ± 0.46	3.0 ± 0.3	- 0.88 ± .25
ETN <sub>2</sub>	0.05	0.16 ± 0.06	+ 0.11 ± .06	0.05	0.25 ± 0.17	+ 0.20 ± .16
PAP	13.7 ± 3.2	21.0 ± 6.0	+ 7.3 ± 4.5	14.3 ± 2.3	27.7 ± 11.5	+ 13 ± 12.2
MAP	129 ± 18	121 ± 24	- 8 ± 6	118 ± 33	107 ± 32	- 11 ± 11

<sup>a</sup>The mean change (Δ) in each parameter is shown. All values are means ± SD.

<sup>b</sup>At time of maximum alteration after injection.

stable. The mean PaCO<sub>2</sub> (± SD) at which the 30 injections were performed was 31.5 ± 6.3 mm Hg. The serial air injections were well tolerated and PAP, ETN<sub>2</sub>, and ETCO<sub>2</sub> values consistently returned to stable preinjection values. In one instance (a 1.5 ml/kg injection) it was necessary to extend the interinjection interval to 40 min to allow recovery of PAP to baseline (34 min).

The data regarding the frequency of positive responses to each air injectate volume yielded by the three techniques are presented in Table 1. The percentage of positive responses for the three techniques was not different for any volume of injectate. Positive responses were not invariably observed for all three methods until injectate volumes reached 1 ml/kg. The mean changes in PAP, ETCO<sub>2</sub>, and ETN<sub>2</sub> observed after 1.0 and 1.5 ml/kg injections (the 100% response levels) are shown in Table 2. The times required for each variable to reach a maximum change and to recover to a stable baseline after the 1.0 and 1.5 ml/kg injections are given in Table 3. The times required to achieve the maximum response for the 1.0 and 1.5 ml/kg injections were not different for PAP and ETN<sub>2</sub>. Both PAP ( $P < .001$ ) and ETN<sub>2</sub> and ( $P < .002$ ) achieved maximum values more rapidly than ETCO<sub>2</sub>, although the range was narrow and the response of all three techniques was consistently rapid, e.g., at 1.0 ml/kg—ETN<sub>2</sub> 1.25 ± 0.5 min, PAP 1.35 ± 1.5 min, and ETCO<sub>2</sub> 2.10 ± 1.1 min. The sequence in which the three techniques returned to stable baseline values was in every instance ETN<sub>2</sub>, ETCO<sub>2</sub>, PAP. The differences in time to baseline for PAP and ETCO<sub>2</sub> were small but statistically significant ( $P < .001$ ), and ETN<sub>2</sub> was considerably more rapid than either ETCO<sub>2</sub> or PAP ( $P < .001$ ), e.g., for 1.0 ml/kg: ETN<sub>2</sub> 8.5 ± 3.9, ETCO<sub>2</sub> 15.3 ± 2.1, and PAP 19.7 ± 3.5 min.

## Discussion

Our data indicate that ETN<sub>2</sub> is within the same order of sensitivity as PAP and ETCO<sub>2</sub> in the detection of venous air embolism. Because the method is nonin-

vasive, quantitative (1), and potentially specific for VAE, ETN<sub>2</sub> analysis might therefore appear to offer some advantage over the other two techniques. However, the magnitude of the ETN<sub>2</sub> increments involved (e.g., 0.11% for a 1.0 ml/kg injection) probably represents a major limitation in the effective application of this method. Apart from demanding absolute freedom from air contamination of the ventilator and anesthetic circuit, the method requires that the nitrogen analysis system achieve a very high level of sensitivity. While the instrument that we employed is capable of detecting increments in ETN<sub>2</sub> of less than 0.04% (our definition of a positive response), there was technical difficulty in achieving this level of sensitivity in the experimental setting. The difficulty arose because the nitrogen detection plate in this type of mass spectrometer "sees" carbon dioxide as nitrogen. (For the instrument that we employed, a 1.0% increase in CO<sub>2</sub> concentration resulted in an increase in "nitrogen" concentration as registered at the collecting plate of 0.08%.) This type of mass spectrometer is equipped with compensation circuits that apply a correction to the registered nitrogen value that is proportional to the simultaneously recorded CO<sub>2</sub> concentration. The accuracy of this correction would be less critical if ETCO<sub>2</sub> were a constant during VAE-related changes in ETN<sub>2</sub>. But, after VAE, both ETN<sub>2</sub> and ETCO<sub>2</sub> change simultaneously. Although the CO<sub>2</sub>/N<sub>2</sub> compensation performed by our instrument was more than adequate for most uses, it was not sufficiently accurate for this application and we circumvented it as described in the methods section. Instruments intended for the detection of VAE under clinical circumstances will require very precise corrections for the interaction of carbon dioxide (as well as nitrous oxide) on the nitrogen collector.

Differences in the temporal pattern of the response and recovery of PAP, ETCO<sub>2</sub>, and ETN<sub>2</sub> after VAE may indicate another limitation of ETN<sub>2</sub> monitoring. PAP and ETN<sub>2</sub> consistently reached the maximum change after VAE more rapidly than did ETCO<sub>2</sub>, although the responses of all three techniques were sufficiently

Table 3. Times (min  $\pm$  sd) Elapsed between Air Injection and Maximum Changes, and between Air Injection and Return to Baseline Values for Pulmonary Artery Pressure (PAP), End-Tidal CO<sub>2</sub> (ETCO<sub>2</sub>), and End-Tidal N<sub>2</sub> (ETN<sub>2</sub>)

Volume injected	Time to maximum change		Time to baseline	
	1.0	1.5	1.0	1.5
PAP	1.35 $\pm$ 1.5	0.92 $\pm$ 0.7 <sup>a</sup>	19.7 $\pm$ 3.5	23.8 $\pm$ 6.1 <sup>a,b</sup>
ETCO <sub>2</sub>	2.10 $\pm$ 1.1	1.85 $\pm$ 0.7 <sup>a</sup>	15.3 $\pm$ 2.1	19.4 $\pm$ 6.0 <sup>a</sup>
ETN <sub>2</sub>	1.25 $\pm$ 0.5	1.20 $\pm$ 0.5	8.5 $\pm$ 3.9	8.0 $\pm$ 4.3

<sup>a</sup>PAP significantly different from ETCO<sub>2</sub> ( $P < 0.001$ ).

<sup>b</sup>PAP significantly different from ETN<sub>2</sub> ( $P < 0.001$ ).

<sup>c</sup>ETCO<sub>2</sub> significantly different from ETN<sub>2</sub> ( $P < 0.002$ ).

prompt that latency of response need not be a consideration in choosing among these methods. By contrast, differences in the times required for return to the pre-VAE baseline values may indicate a matter of clinical importance. ETN<sub>2</sub> values consistently fell to levels indistinguishable from baseline more rapidly than either PAP or ETCO<sub>2</sub>. It has been suggested that it is important to employ a monitoring technique that not only gives an indication of air entry, but also provides evidence of either the persistence in or clearance from the pulmonary circulation of the entrained air (5). The persistent elevation of PAP and depression of ETCO<sub>2</sub> when ETN<sub>2</sub> had returned to baseline may therefore point to a shortcoming of ETN<sub>2</sub> measurement. These differences in the time for return to baseline may represent the presence of air that is "held up" in larger pulmonary vessels and that is being delivered to the alveolus too slowly to permit detection. Lechner et al.(6) suspected this phenomenon as the explanation for their inability to recover more than 60% of intravenously injected air from expired gases, and they provided supportive evidence by demonstrating elevation of PAP after an exposure to 75% nitrous oxide initiated immediately after cessation of detectable nitrogen excretion. The data presented herein suggest that even when ETN<sub>2</sub> has fallen to baseline values, a degree of pulmonary vascular obstruction with concomitant circulatory compromise may persist, and that exposure to the risk of further VAE events may not yet be appropriate. Confirmation that a degree of circulatory compromise existed at the time of the return of ETN<sub>2</sub> values to baseline would have required measurements of hemodynamic function (cardiac output, pulmonary artery occlusion pressure, systemic vascular resistance, pulmonary vascular resistance) at that point. The observed differences in time to baseline were not anticipated, and those measurements were not performed.

As indicated above, the increases in ETN<sub>2</sub> that we observed after VAE were small. They were smaller than the increases in ETN<sub>2</sub> observed after experimen-

tal VAE in a study performed in another laboratory. Losee et al.(1) injected air into the right ventricle of pentobarbital-anesthetized dogs. For an injectate volume of 1 ml/kg, they observed an ETN<sub>2</sub> increase of approximately 0.2% whereas in our study the injection of the same volume of air resulted in a 0.11% elevation. Several factors may have contributed to this difference.

- 1) Alveolar ventilation. The animals in the study of Losee et al.(1) were normocapnic, and those in this study were hyperventilated in an attempt to imitate the common neurosurgical setting. The greater alveolar ventilation in our study would have had the effect of "diluting" any nitrogen entering the alveoli in a larger volume of alveolar ventilation with, as a result, a lower peak nitrogen concentration in each expired breath.
- 2) Delayed delivery of air to the pulmonary vasculature. Two factors may have contributed to a protracted delivery of air to the microvasculature of the lung and a concomitant reduction in peak ETN<sub>2</sub> values. First, the injections in the Losee study (1) were probably made into the right ventricle (6). In the present study, the air was injected into the jugular venous system. The latter may have delayed delivery of air to the pulmonary vasculature because air injected into the jugular vein may have become temporarily delayed in the superior vena cava (7-9), and because air injected into the jugular vein may have, in some instances, crossed a patent foramen ovale to the left heart. A patent foramen ovale is known to occur in dogs (10) though the incidence, to our knowledge, is undefined. Second, the caliber of the route through which air was injected was larger in the present study. Virtue et al.(11) demonstrated a delay prior to the appearance of bubbles in the pulmonary microcirculation following injection of air into the right ventricle. This delay may reflect the trapping of air at more proximal bifurcations (12) and the need to fragment larger bubbles to permit their delivery to smaller, more distal vessels. The air in the present study was injected through an 18-gauge catheter (diameter, 1.24 mm), and in the study of Losee et al.(1) via an orifice of 0.74 mm diameter. Our larger gauge air injection route may have resulted in larger bubbles, and thereby contributed to a more protracted delivery of air to perialveolar vessels.

Note that if the total volume of expired nitrogen, instead of merely peak ETN<sub>2</sub> values, had been measured, the discrepancies occasioned by the various methodologic differences listed above should be eliminated. However, in the present study only end-tidal concentrations were measured.



It is likely that the capacity of our study to detect subtle differences in the VAE detection sensitivity of PAP,  $\text{ETCO}_2$ , and  $\text{ETN}_2$  was restricted by the limited number of dogs studied ( $n = 6$ ). Nonetheless, it appears that, when the nitrogen analysis technique can reliably detect  $\text{ETN}_2$  changes on the order of 0.04%, the sensitivity of  $\text{ETN}_2$  as an indicator of VAE is of at least a similar order to that of PAP and  $\text{ETCO}_2$ . However, in spite of the theoretical appeal of  $\text{ETN}_2$  analysis and the relative level of sensitivity that this study has identified, the role of  $\text{ETN}_2$  measurement in the detection of VAE under clinical conditions is probably limited. The extremely low concentrations of nitrogen involved require both a very high level of nitrogen detection sensitivity and stringent avoidance of contamination by environmental nitrogen in order to identify reliably anything less than catastrophic VAE. Accordingly, it appears unlikely that  $\text{ETN}_2$  analysis can function currently as "an early warning system" in the detection of VAE. Furthermore the data suggest that  $\text{ETN}_2$  may overestimate the rate of clearance of air from the pulmonary vasculature, and this represents a limitation in the use of this method in decision making concerning resumption of the head-up posture and surgery after an episode of VAE.

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## Cardiac Electrophysiologic Effects of Pancuronium

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JACOBS HK, LIM S, SALEM MR, RAO TLK, MATHRU M, SMITH BD. Cardiac electrophysiologic effects of pancuronium. *Anesth Analg* 1985;64:693-9.

*A microelectrode examination of guinea pig left ventricular papillary muscle was performed to determine whether there was a direct effect of pancuronium on cardiac cells and, if so, to attempt to ascertain the mechanism of this effect. Electrical events were measured before and during superfusion with pancuronium, epinephrine, propranolol, and verapamil; alone and in various combinations. Pancuronium prolonged the duration of the action potential (AP); increased resting potential (Em), AP magnitude, and rate of rise of the AP (dV/dt); and resulted in spontaneity in*

*12% of the muscles. Epinephrine and pancuronium combined caused spontaneity in 80% of the muscles and oscillatory behavior. Additionally, this combination decreased AP magnitude, Em, and dV/dt in several preparations—a pattern of response similar to that seen in ouabain-treated myocardial cells under the influence of catecholamines. These changes were always reversed by verapamil or by perfusion with a drug-free medium, and were usually reversed by propranolol. The data suggest a combined pancuronium/epinephrine induced increase in cardiac membrane permeability to  $Ca^{2+}$ .*

**Key Words:** NEUROMUSCULAR RELAXANTS—pancuronium. HEART—pancuronium effects.

Since the clinical introduction of pancuronium bromide, a nondepolarizing muscle relaxant, many reports have appeared citing the cardiovascular effects of this relaxant (1-3). The hemodynamic changes, usually minimal, have been well documented (3), but there are occasional reports citing more major adverse cardiac effects, including excessive sinus tachycardia, bigeminy, premature ventricular contractions, and nodal rhythms (1,4,5). Other reports cite additional changes in myocardial activity correlated with the administration of pancuronium (6-8).

The implication that pancuronium causes dysrhythmias has been prevalent for a number of years (3) without either cause or mechanism being defined. Dysrhythmias have, however, occasionally been treated successfully with propranolol, suggesting that sympathetic influences or changes in  $Ca^{2+}$  flux may be involved. Other hypotheses that have been advanced

to explain these myocardial effects range from the blocking of cardiac muscarinic receptors (9) to sympathetic ganglia stimulation (2). However to date, a direct effect of pancuronium on the electrical characteristics of heart cells has not been demonstrated. It was the purpose of this study to determine whether there was such a direct effect and, if so, to determine the mechanism of this effect.

### Methods

A standard microelectrode examination of guinea pig left ventricular papillary muscle was carried out. Briefly, an animal was anesthetized with 30 mg/kg sodium pentobarbital. The thorax was opened and the heart was rapidly removed and placed in oxygenated Krebs fluid at room temperature. The ventricular cavity was opened and the anterior papillary muscle dissected free. Cordae and part of the valve were left attached at the basal end, and a small section of ventricular wall was left attached at the apical end. These tissues served as the sites of clamping when the muscle was isometrically mounted at approximately in situ length in a constant temperature chamber.

Constant perfusion at pH 7.40 and  $30.0 \pm 0.5^\circ\text{C}$  was maintained with a solution of the following mM composition: NaCl, 119.2; KCl, 3.0;  $\text{KH}_2\text{PO}_4$ , 1.0;  $\text{MgSO}_4$ , 1.0;  $\text{NaHCO}_3$ , 26.3;  $\text{CaCl}_2$ , 2.8; and dextrose, 11.1. This modified Krebs solution was oxygenated

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with a water-saturated 95% O<sub>2</sub>-5% CO<sub>2</sub> mixture. It has been shown elsewhere that this technique is adequate to maintain viable and stable electrical and mechanical properties for at least 6 hr (10,11). The preparations were paced at 60 beats/min, or at just capture rate if the muscles were spontaneously contracting at a rate greater than 60 beats/min. An hour was allowed at these conditions for equilibration before penetration with glass microelectrodes was attempted. The electrodes, filled with 3M KCl, had resistances of from 5 to 20 mΩ.

A cell was impaled after the equilibration period, and the electrical characteristics were monitored until action and resting potentials were constant (within 2 mV) for 3 min. This was taken as baseline. A step change was then made by adding pancuronium, epinephrine, or both to the bath and to the perfusion solution reservoir. Any changes that might occur were allowed to reach completion, or a maximum of 20 min, at which time either propranolol or verapamil was added to the bathing solution, or the baseline conditions were reestablished. Only data derived from electrode penetration of a cell maintained throughout the entire period of study were tabulated.

The concentration of pancuronium used ( $1.4 \times 10^{-6}$  M) was extrapolated from a clinical dosage of 0.1 mg/kg. Epinephrine was used at  $5.5 \times 10^{-6}$  M, a dose found to induce spontaneity in about 35% of the preparations under the conditions of these experiments. Propranolol was added at  $3.4 \times 10^{-6}$  M (approximately equivalent to an in situ dose of 0.5 mg/kg). Verapamil, an antidysrhythmic cardiac drug considered a specific calcium (or slow channel) blocker (12) was used at 0.2 μg/ml ( $4.1 \times 10^{-7}$  M).

Measured variables included transmembrane resting potential (Em), the magnitude of the action potential (AP), the rate of rise of phase 0 of the action potential ( $dV/dt$ ), and the 50 and 90% action potential durations. All waveforms were displayed on a storage oscilloscope and photographed. Data were tabulated from enlarged prints of the 35-mm film. In addition, the action potentials were examined for qualitative configurational changes. Any changes in frequency of contraction due to increased spontaneity were also noted.

The eighteen papillary muscles used in this study were found to be viable by a preliminary microelectrode examination of several cells from each muscle and by visual observation of contractions. A single cell with a resting potential representative of the entire muscle was then impaled for thorough study. Usually only one cell was completely studied per muscle preparation to eliminate the possibility of prolonged effects of any intervention. In a few selected

Table 1. Transmembrane Electrical Recordings (mean  $\pm$  SEM) before and during Pancuronium ( $1.4 \times 10^{-6}$  M) Superfusion of Guinea Pig Papillary Muscle at 30°C, pH 7.40

	Baseline	Pancuronium
50% duration (msec)	86.4 $\pm$ 11.6 ( <i>n</i> = 20)	96.2 $\pm$ 11.6 <sup>a</sup>
90% duration (msec)	121.8 $\pm$ 11.5 (20)	132.4 $\pm$ 11.2 <sup>a</sup>
AP magnitude (mV)	107.3 $\pm$ 2.8 (20)	116.6 $\pm$ 1.9 <sup>b</sup>
Em (mV)	-81.9 $\pm$ 1.1 (21)	-84.0 $\pm$ 1.4 <sup>a</sup>
$dV/dt$ (V/sec)	62.2 $\pm$ 3.2 (17)	68.2 $\pm$ 4.4 <sup>a</sup>

Numbers in parentheses indicate number of cells studied.

<sup>a</sup>*P* < 0.05 pancuronium vs baseline data as determined by paired *t*-test.

<sup>b</sup>*P* < 0.01 pancuronium vs baseline data as determined by paired *t*-test.

muscle preparations as many as three cells were studied, with a recovery period of 0.5-1 hr allowed between the study of any two cells.

Data were analyzed through the use of the *t*-test for paired data or by  $\chi^2$ -analysis as indicated. A *P* value of 5% or less was considered statistically significant. Data are presented as the mean values  $\pm$  SEM.

## Results

Table 1 presents the data derived during steady-state baseline conditions and at the time of maximum change after the addition of  $1.4 \times 10^{-6}$  M pancuronium to the perfusion solution. Both the 50 and 90% durations of the AP increased significantly. The magnitude of these changes was approximately 10 msec in each case. The AP magnitude and  $dV/dt$  also showed significant increases. In addition, the Em increased significantly, becoming approximately 2 mV more negative after pancuronium. Representative oscilloscopic tracings of the action potentials of a single cell are shown in Figure 1, where a broadening of the plateau of the action potential can be seen after pancuronium administration.

Once the effects of pancuronium had reached their maxima, either propranolol or verapamil was added to the perfusing solution. Under these conditions, both were without effect (Tables 2,3).

The individual and combined effects of pancuronium and epinephrine on automaticity, as evidenced by the muscles achieving a spontaneous frequency of contraction above the pacing rate, are shown in Table 4. Pancuronium alone increased spontaneity in 12% of the preparations. Epinephrine caused 3 of 8 muscles (37.5%) to exceed the 60 beats/min driving rate. The combination of pancuronium and epinephrine was more than additive, and resulted in increased automaticity in 12 out of 15 preparations (80%).

In the 12 preparations that achieved an increased automaticity after pancuronium and epinephrine, two

**Table 2.** Transmembrane Electrical Recordings (mean  $\pm$  SEM) of Guinea Pig Papillary Muscle at 30°C, pH 7.40, before and during the Addition of Pancuronium ( $1.4 \times 10^{-6}$  M) to the Perfusion Solution, and during the Further Addition of Propranolol ( $3.4 \times 10^{-6}$  M) to the Perfusion Solution ( $n = 4$ )

	Baseline	Plus pancuronium	Plus propranolol <sup>a</sup>
50% duration (msec)	114.7 $\pm$ 10.0	135.0 $\pm$ 9.5	146.3 $\pm$ 16.9
90% duration (msec)	149.7 $\pm$ 6.6	166.7 $\pm$ 12.2	176.7 $\pm$ 16.9
AP magnitude (mV)	119.7 $\pm$ 8.3	122.3 $\pm$ 6.7	117.7 $\pm$ 7.9
Em (mV)	-83.3 $\pm$ 4.2	-86.3 $\pm$ 2.2	-82.3 $\pm$ 2.9
dV/dt (V/sec)	59.8 $\pm$ 14.3	69.5 $\pm$ 14.3	62.5 $\pm$ 11.4

<sup>a</sup>All comparisons, pancuronium vs propranolol data, are not significant as determined by paired *t*-test.

**Table 3.** Transmembrane Electrical Recordings (mean  $\pm$  SEM) of Guinea Pig Papillary Muscle at 30°C, pH 7.40, before and during the Addition of Pancuronium ( $1.4 \times 10^{-6}$  M) to the Perfusion Solution, and during the Further Addition of Verapamil ( $4.1 \times 10^{-7}$  M) to the Perfusion Solution ( $n = 5$ )

	Baseline	Plus pancuronium	Plus verapamil <sup>a</sup>
50% duration (msec)	98.8 $\pm$ 35.8	104.2 $\pm$ 34.3	97.2 $\pm$ 35.7
90% duration (msec)	132.6 $\pm$ 34.7	138.2 $\pm$ 40.0	135.1 $\pm$ 33.4
AP magnitude (mV)	116.0 $\pm$ 4.9	120.8 $\pm$ 1.7	112.2 $\pm$ 3.4
Em (mV)	-83.0 $\pm$ 2.3	-84.0 $\pm$ 1.9	-82.8 $\pm$ 2.5
dV/dt (V/sec)	54.3 $\pm$ 12.1	63.7 $\pm$ 9.5	58.1 $\pm$ 11.3

<sup>a</sup>All comparisons, pancuronium vs verapamil data are not significant as determined by paired *t*-test.

distinct response patterns were apparent (Table 5). One group of 4 had frequencies of contraction of  $81 \pm 14$  beats/min (pattern A, Table 5). The other group (pattern B, Table 5) had frequencies of contraction approaching 200 beats/minute, marked decreases in Em and AP magnitude, and a decreased dV/dt.

For the 4 muscles following pattern A, no striking changes were noted in the AP. They were qualitatively normal even though the AP magnitude increased significantly after combined pancuronium and epinephrine. Durations are not presented because at higher frequencies of contraction comparison to baseline values is not valid.

In the 8 remaining preparations (pattern B, Table 5), striking changes were seen, and 3 of these 8 muscles were monitored with a continual microelectrode penetration. These 3 preparations showed frequencies of contraction of  $196 \pm 27$  beats/min. Although the remaining 5 preparations could not be monitored throughout the entire course of the interventions, there were indications that these muscles followed pattern B closely before electrode penetration was lost.

The 3 muscle cells that could be monitored showed a highly significant decrease in Em, with simultaneous decreases in AP magnitude and dV/dt. The height of the AP only matched the Em, and no overshoot existed. Mean dV/dt decreased to 10.2 V/sec, just over 20% of the control value. Figure 2 shows driven action potentials from the same cell under baseline condi-

**Table 4.** Papillary Muscle Preparations Achieving a Spontaneous Frequency of Contraction Greater than the 60 beats/min Driving Rate Due to a Step Change from Baseline Conditions to the Listed Intervention

Intervention	Preparations achieving frequency > 60 beats/min	Total trials	% Spontaneity
Pancuronium ( $1.4 \times 10^{-6}$ M)	3	25	12.0 <sup>a</sup>
Epinephrine ( $5.5 \times 10^{-6}$ M)	3	8	37.5 <sup>b</sup>
Combined pancuronium plus epinephrine (same doses)	12	15	80.0

<sup>a</sup> $P < 0.005$  from the combined intervention data as determined by the  $\chi^2$ -test.

<sup>b</sup> $P < 0.025$  from the combined intervention data as determined by the  $\chi^2$ -test.

tions (upper panel) and after the combined administration of pancuronium and epinephrine (lower panel). Oscillatory behavior occurred in the resting potential of this cell (and others) as can be seen more clearly in the lower panel of Figure 3. Action potentials arose, apparently in a coupled fashion, from these oscillations.

Attempts to convert the low Em, the low and slow AP, oscillatory behavior, and high spontaneous frequencies of contraction caused by pancuronium and



Table 5. Two Patterns of Transmembrane Electrical Change (mean  $\pm$  SEM) following the Addition of Pancuronium ( $1.4 \times 10^{-6}$  M) Plus Epinephrine ( $5.5 \times 10^{-6}$  M) to the Perfusion Solution in Guinea Pig Papillary Muscle at 30°C, pH 7.40

Variable	Pattern A (frequency of contraction = $81 \pm 14$ beats/min, $n = 4$ )		Pattern B (frequency of contraction = $196 \pm 27$ beats/min, $n = 3$ )	
	Baseline	Intervention	Baseline	Intervention
AP (mV)	$110.3 \pm 5.6$	$114.0 \pm 2.1^*$	$110.0 \pm 6.0$	$69.0 \pm 1.0^a$
Em (mV)	$85.0 \pm 4.0$	$-85.3 \pm 2.7$	$-88.0 \pm 2.1$	$-69.4 \pm 2.7^b$
$dV/dt$ (V/sec)	$52.1 \pm 4.8$	$50.8 \pm 3.6$	$47.5 \pm 2.9$	$10.2 \pm 4.4^c$

See text for description of the different patterns.

<sup>a</sup> $P < 0.05$  vs baseline by paired  $t$ -test.

<sup>b</sup> $P < 0.01$  vs baseline by paired  $t$ -test.

<sup>c</sup> $n$  = number of cells studied.

epinephrine toward the baseline pattern were made four times by the addition of propranolol to the perfusing solution, five times by adding verapamil, and four times by perfusion with drug-free solution. Conversion was successful in every instance except for one attempt after perfusion with propranolol. It was necessary to perfuse this muscle with drug-free solution before conversion was successful. The pattern of conversion in a given muscle preparation can be ascertained by observation of Figures 2 through 4.

## Discussion

The present data show that pancuronium causes changes in the electrical function of myocardial cells. Increases in action potential magnitude and  $dV/dt$ , the more negative resting potential, and the increased 50 and 90% action potential durations suggest a non-specific membrane change involving  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{2+}$ .

Although these changes were statistically significant, the physiologic significance is questionable. The increased negativity of the Em may cause a slight decrease in excitability, or a slight increase in AP height, or both (13). Because the magnitude of change in Em was small, however, the changes seen on phase 0 might more readily be accounted for by an increased  $\text{Na}^+$  flux. The increase in AP magnitude and  $dV/dt$ , both indicative of greater sodium entry into the cell (13), can increase conduction velocity (14,15) and contractile strength (16). The increased calcium fluxes suggested by the increased action potential durations may or may not be of importance in contractility changes. This would depend on whether enough additional calcium ion can cross the myocardial membrane, or be released from intracellular stores (17) during the 10% increment in duration, to be effective in causing a measurable increase in tension produc-

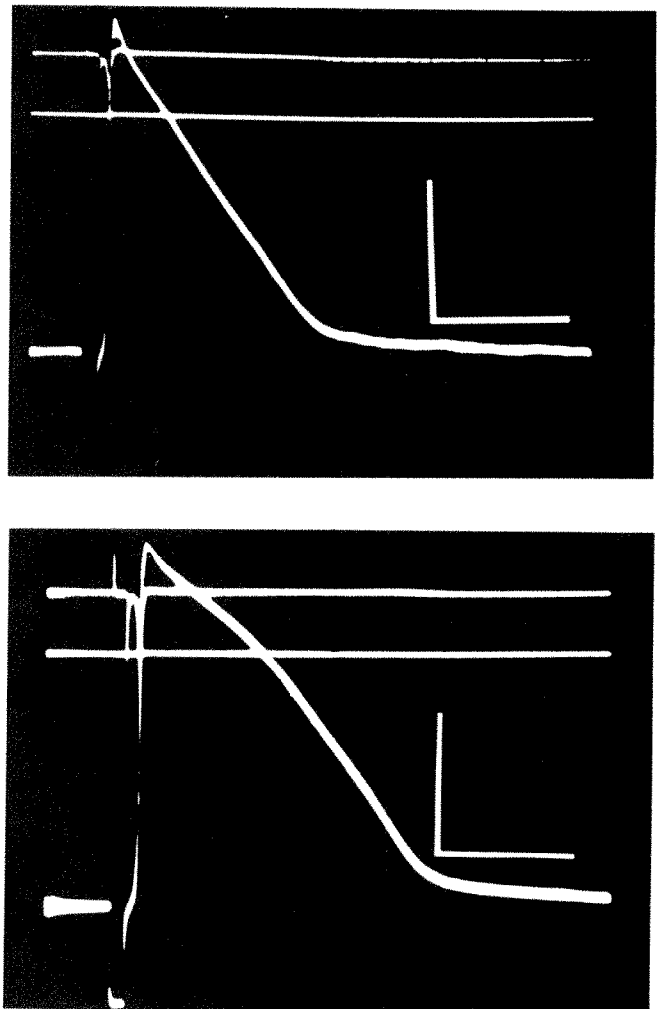
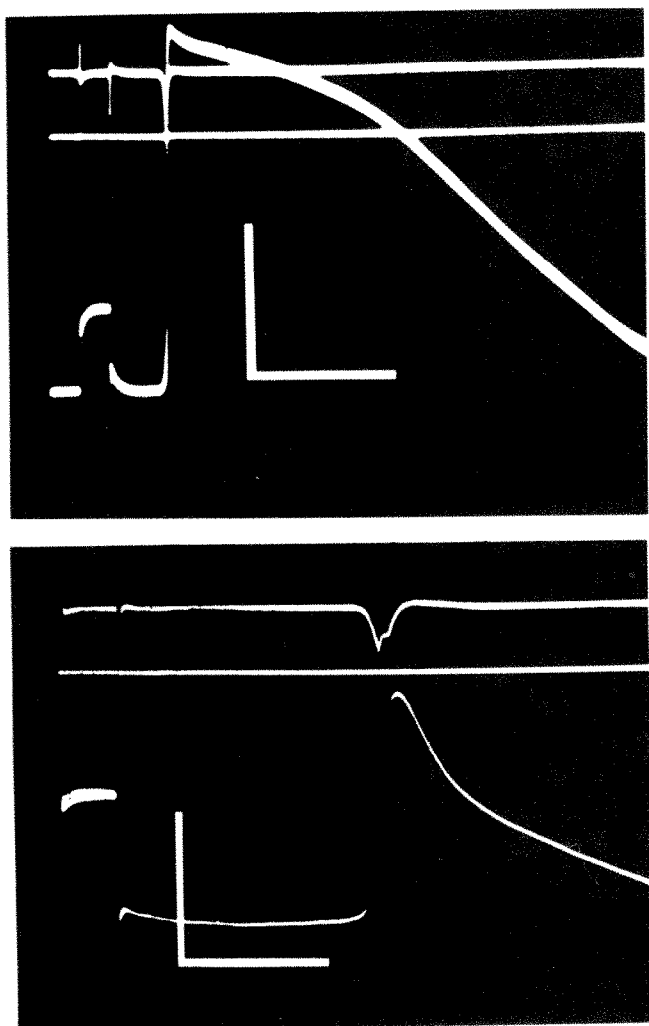


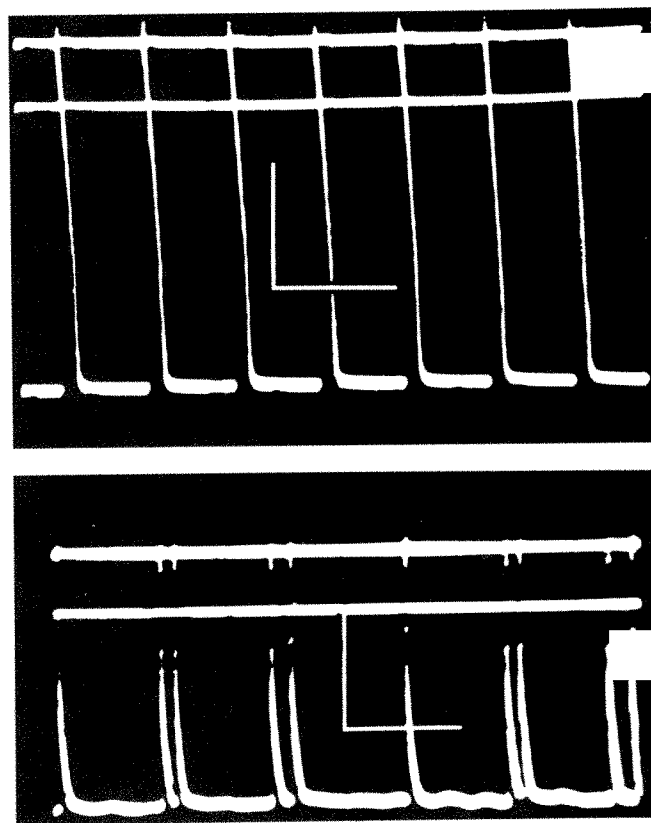
Figure 1. Driven action potentials of papillary muscle cell under baseline conditions (upper panel) and 18 min after superfusion with  $1.4 \times 10^{-6}$  M pancuronium bromide (lower panel). Calibration scales are 50 mV and 50 V/sec (vertical) and 50 msec (horizontal). The upper trace in each panel is  $dV/dt$ ; middle trace—zero potential line; lower trace—transmembrane potential. The stimulus artifact is seen to the left of the upstroke of the action potential in both cases.



**Figure 2.** Action potentials of papillary muscle cell before (upper panel) and 7 min after superfusion with pancuronium bromide ( $1.4 \times 10^{-6}$  M) plus epinephrine ( $5.5 \times 10^{-6}$  M) (lower panel). Calibration scales for upper panel—50 mV and 50 V/sec (vertical) and 40 msec (horizontal); lower panel—50 mV and 50 V/sec (vertical) and 20 msec (horizontal). The upper trace in each panel is  $dV/dt$ ; middle trace—zero potential line; lower trace—transmembrane potential. Both panels were electrically driven at 72 beats/min.

tion and the kinetics thereof. This seems unlikely, and all of these generalized changes probably have only minimal effects on normal cardiac contractility.

Of greater importance is the finding of an increased automaticity under certain conditions. In order to determine whether or not pancuronium increased automaticity in the myocardium, any increase in the frequency of contraction over the driving frequency was tabulated. The muscle preparations tested in this series of experiments had potentially automatic fibers. Fibers in the valve leaflets, left attached at the basal end of the muscle, as well as Purkinje fibers, are both capable of phase 4 depolarization (12). Our empiri-



**Figure 3.** Driven action potentials (capture rate, 72 beats/min) of papillary muscle cell under baseline conditions (upper panel; same cell as Figure 2, different sweep speed) and after superfusion with pancuronium bromide ( $1.4 \times 10^{-6}$  M) (lower panel—taken 2 min after the lower panel of Fig. 2). Calibration scales are 50 mV and 50 V/sec (vertical) and 100 msec (horizontal).

cally utilized pacing rate (frequency of electrical stimulation of the muscles) was a moderately low 60 beats/min. Any spontaneous increase over this frequency was defined as an elevated automaticity. Because we did not see any true pacemaker cells by actual microelectrode penetration, it is not possible to state whether the increase in frequency of muscle contractions was due to true pacemaker type activity, to a form of reentry, or, quite likely from the oscillatory behavior that was observed, to triggered activity (18). In any event, the fact that verapamil (and usually propranolol) could block or reverse the increased rates, particularly in the presence of a catecholamine, argues that the ionic species primarily responsible for the increased rates and membrane oscillation is  $\text{Ca}^{2+}$ .

The data seen after pancuronium and epinephrine superfusion (Table 5, pattern B) are important in this regard. The low resting potentials, low action potentials, and low rates of rise are all strongly suggestive of  $\text{Ca}^{2+}$  or slow type action potentials (12). It has been shown that this type of AP can occur not only in nodal

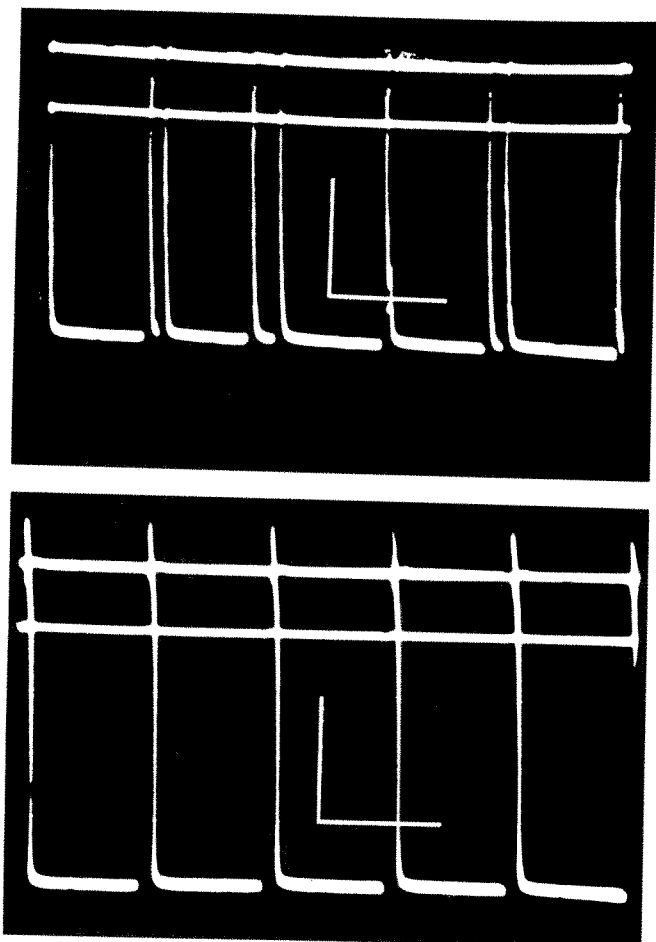


Figure 4. Action potentials from same cell as in Figures 2 and 3, taken 4 min after beginning washout to baseline conditions (upper panel) and 7 min later (lower panel). Calibration scales are 50 mV and 50 V/sec (vertical) and 1000 msec (horizontal). Both panels driven at 60 beats/min.

tissue but also in working musculature (19). In the present study, the myocardial muscle cells into which microelectrodes were placed were assumed to be free of hypoxia or other extraordinary conditions. Nevertheless, under the influence of the relaxant and the catecholamine, a highly abnormal type of action potential was observed. These action potentials did not appear to be "pure"  $\text{Ca}^{2+}$  action potentials, but rather, due to their configuration, appeared to be of an intermediate  $\text{Na}^{+}$ - $\text{Ca}^{2+}$  type. Similar types of action potentials have been reported with digitalized preparations with or without catecholamines (20,21). One might speculate that even more pronounced changes occur in myocardial cells normally considered to be either slow fibers or excitable cells.

These data are consistent with recent reports regarding the effects of pancuronium on the heart (22,23). The mechanisms for the myocardial effects of pancuronium could be either a direct membrane effect,

as demonstrated by our nonspecific membrane changes, or be related to an increase in activity of the sympathetic nervous system. Enhanced release of catecholamines, prevention of reuptake (24), or sympathetic-parasympathetic interactions (25) are all possible. Any of the above could explain why  $\beta$ -receptor blockade inhibited the cardiac effects of pancuronium.

In summary, pancuronium, particularly in the presence of epinephrine or perhaps coupled with high sympathetic nervous system activity, causes changes in myocardial electrical activity. The most important of these changes are conversion of fast action potentials to intermediate or slow action potentials and the appearance of oscillatory membrane potentials. Such changes can lead to ectopic rhythms and severe tachycardia. Reversal of these changes is possible with propranolol or verapamil. Thus we feel that pancuronium should be used with caution in situations in which cardiac dysrhythmias are likely.

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## Incidence of Malignant Hyperthermia in Denmark

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ØRDING H. Incidence of malignant hyperthermia in Denmark. *Anesth Analg* 1985;64:700-4.

*Questionnaires were sent to all anesthesia departments in Denmark to determine the total number of anesthetics given per year, and the distribution of different types of anesthesia. All cases of suspected malignant hyperthermia forwarded to the Danish Malignant Hyperthermia Register during a 6.5 yr period were reviewed and divided into subgroups according to clinical criteria. The incidence of suspected malignant hyperthermia in these subgroups was calculated in relation to type of anesthesia. The results are based on information about 386,250 anesthetics and 154 cases of sus-*

*pected malignant hyperthermia. All cases of malignant hyperthermia occurred during general anesthesia, and more than 75% during anesthesia with a combination of potent inhalation agents and succinylcholine. The incidence of fulminant malignant hyperthermia was low: 1 in 250,000 total anesthetic procedures, but 1 in 62,000 anesthetic procedures with a combination of potent inhalation agents and succinylcholine. Masseter spasm occurred in 1 of 12,000 anesthetic procedures in which succinylcholine was administered. Suspicion of malignant hyperthermia was raised in 1 of 16,000 anesthetics total, but in 1 of 4,200 anesthetics with the above-mentioned combination of agents.*

**Key Words:** HYPERTHERMIA—malignant.

The incidence of malignant hyperthermia (MH) is not known, but estimates vary between 1 in 14,000 (1) and 1 in 200,000 anesthetics (2). This discrepancy may be partly explained by the lack of uniform criteria for the clinical diagnosis of MH and partly by variation in the types of anesthesia used.

In 1977 the Danish Malignant Hyperthermia Register was established (3). One of the purposes of this unit was to collect information about MH in Denmark. Anesthesiologists in Denmark were asked to forward information to the register about fulminant and suspected cases of MH. Since 1978 the number of cases of MH reported per year has been fairly stable. Therefore it was considered appropriate to examine the incidence of various forms of clinical MH. However, the total number of anesthetics given per year in Denmark (5 million inhabitants) was not known, nor was the distribution of different anesthetic techniques. Therefore, the purpose of this study was to collect data on anesthetic practice in Denmark and, using these data, to calculate the incidence of fulminant and abortive forms of MH in relation to different types of anesthesia.

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### Methods

For the evaluation of anesthetic practice in Denmark, 87 questionnaires were sent to all anesthesia departments and to other departments where anesthetics are administered. Questions included the following: total number of anesthetics administered per year; numbers of general and regional anesthetics; number of general anesthetic procedures in which potent inhalation agents were used; number of anesthetic procedures in which succinylcholine was given; and number of anesthetic procedures in which both a potent inhalation agent and succinylcholine were given. If no exact data on these questions existed or could be calculated, the departments were asked to estimate the numbers from knowledge of routine procedures at the department.

For calculation of the annual MH rate, all cases of suspected MH reported to the Danish Malignant Hyperthermia Register from January 1, 1978 to July 1, 1984 (6.5 yr) were reviewed. The cases were divided into two groups. The first group consisted of cases of fulminant MH, in which significant symptoms and signs of MH were seen, such as a rapid increase in body temperature or a measured body temperature above 39.5°C combined with each of the following: metabolic and respiratory acidosis in spite of adequate ventilation, tachycardia, arrhythmia, hyperkalemia, marked rise of serum creatine kinase (CK), and myoglobinuria with no other obvious reason for rhabdomyolysis.

Table 1. Total Number of Anesthetic Procedures per yr and Distribution of Different Types of Anesthesia

	Number	% of total numbers of anesthetics	% of general anesthetics
Total number of anesthetics	386,250	100.0%	—
Number of general anesthetics	341,247	88.3%	100.0%
Number of anesthetics with potent inhalation agents	129,982	33.7%	38.1%
With succinylcholine	76,260	19.7%	22.3%
Without succinylcholine	53,722	13.9%	15.7%
Total number of anesthetics with administration of succinylcholine	172,315	44.6%	50.5%

Table 2. Methods Used to Obtain Data of Table 1

	Exact data	Extrapolation from a limited period of time	Estimate
Total number of anesthetics	100%	0%	0%
Number of general anesthetics	70%	24%	6%
Number of anesthetics with potent inhalation agents	60%	21%	19%
With succinylcholine	30%	26%	44%
Without succinylcholine	30%	26%	44%
Total number of anesthetics with administration of succinylcholine	38%	28%	34%

Data are expressed as % of total number of anesthetic procedures per year.

The second group, abortive MH, was divided into three subgroups: a) spasm of masseter muscles combined with mild symptoms and signs suggestive of MH, such as mild increase in temperature (usually to less than 38.5°C but occasionally more), slight metabolic or respiratory acidosis, moderate increases in heart rate and blood pressure, moderate rise of CK, myoglobinuria, or both; b) spasm of masseter muscles without any other symptoms; and c) mild symptoms as above without masseter spasm.

To calculate the incidence of MH, the average number of reported cases of fulminant and abortive MH per yr was used. The distribution of anesthetics as reported by the questionnaires was used to calculate the incidence of MH in relation to the type of anesthesia. For statistical analysis of data the  $\chi^2$ -test was used. *P* values less than 0.05 were considered significant.

## Results

Replies were obtained from all 87 departments. From 85 departments, the answers were based on 1983 data, and from two departments on 1982 data. The total numbers of anesthetics given per year and the distribution of different types of anesthesia are shown in Table 1. Table 2 shows the methods used to obtain the data of Table 1. All departments had exact data

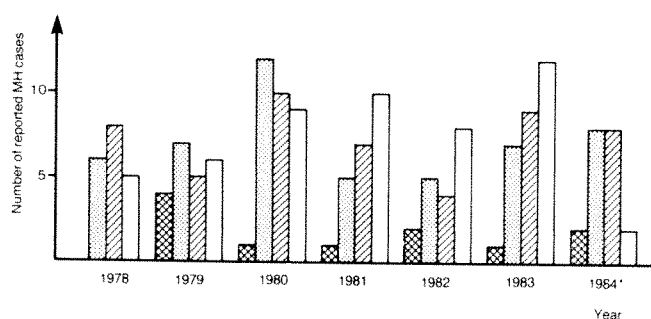
on the total number of anesthetics; less exact information existed on the frequency with which the different types of anesthesia were given (range—68 departments had information on the number of general anesthetics, 39 departments on the combined use of potent inhalation agents and succinylcholine). Thirteen departments, administering 27% of all anesthetics in Denmark, undertook a specific study during a limited period of time (average—1 month) and extrapolated the number of different anesthetic procedures during the period of study to the total number of anesthetic procedures. From the other departments, estimates of the distribution of anesthetic techniques were made based on the routine procedures of anesthesia and type and frequency of operations performed. In Table 3 the distribution of anesthetic methods in the three groups of different data sampling techniques is shown. No statistically significant differences were found among the distributions. The mean distribution of anesthetic methods is shown in Table 1. Halothane was the only potent inhalation agent widely used. Enflurane, isoflurane, and diethyl ether were used less frequently.

During the period from January 1, 1978, to July 1, 1984, 154 cases of suspected MH were reported to the Danish Malignant Hyperthermia Register (Fig. 1). Mean age of the patients was 15 yr (range, 0.5–72). There were 91 males and 63 females ( $\chi^2 = 5.09$ ,  $P < 0.05$ ).

**Table 3.** Distribution of Anesthetic Methods for Different Data Sampling Techniques

	Exact data	Extrapolation from a limited period of time	Estimate
Number of general anesthetics	88.8%	88.2%	84.2%
Number of anesthetics with potent inhalation agents	34.0%	33.2%	33.3%
With succinylcholine	23.2%	18.6%	18.5%
Without succinylcholine	10.8%	14.6%	14.8%
Total number of anesthetics with administration of succinylcholine	47.4%	45.3%	41.9%

All data are expressed as % of total number of anesthetics based on information obtained with each technique. For comparison between distributions  $P > 0.05$ .



**Figure 1.** Number of cases reported to the Danish Malignant Hyperthermia Register during 6.5 yr. ■ fulminant MH; ▨ masseter spasm with mild symptoms of MH; ▤ masseter spasm alone; □ other mild symptoms of MH. The criteria applied in the classification of the patients are described in the text. (\*Extrapolated from data during the first half of 1984.)

Twenty-two of the patients referred to the Danish Malignant Hyperthermia Register in the study period were investigated with muscle biopsy between January 1978 and April 1982 and are reported elsewhere (3).

Ten of the 154 patients (6.5%) had clinically fulminant MH (Table 4). This diagnosis has since been confirmed by muscle biopsy in six of the ten (3); four have not yet had muscle biopsies. One patient died from MH, a mortality rate of 10% in fulminant MH. MH was abortive in 144 patients. The distribution of these 144 patients into subgroups is shown in Table 4. Each subgroup accounted for roughly one-third of the cases of abortive MH. No patient with abortive MH died. All 154 cases of suspected MH occurred during general anesthesia. The type of anesthetic used during a suspected case of MH is shown in Table 5. More than 75% of all cases occurred with the combined use of a potent inhalation agent and succinylcholine. None of the fulminant cases of MH occurred during anesthesia with intravenous agents. The incidence of different forms of MH in relation to type of anesthesia is shown in Table 6. Masseter spasm

occurred in 1 of 12,000 anesthetics in which succinylcholine was used.

## Discussion

In this study the incidence of fulminant MH was found to be 1 in 250,000 anesthetics of all types, and 1 in 220,000 general anesthetics (Table 6). It is obvious from our results that a change in anesthetic practice will significantly change the incidence of MH. Fulminant MH was reported in 1 of 62,000 anesthetics in which both a potent inhalation agent and succinylcholine were administered, whereas no cases were reported after regional or intravenous anesthesia. Although fulminant MH was rarely encountered, suspicion of MH was raised fairly often; masseter spasm was reported in 1 of 12,000 administrations of succinylcholine, and abortive forms of MH in 1 of 4,200 anesthetics in which both potent inhalation agents and succinylcholine were used. Overall, suspicion of MH was raised in 1 of 16,000 anesthetics (Table 6).

These results may partially explain the discrepancies in the reported incidence of MH. Ellis and Halsall reported the incidence in the United Kingdom to be 1 in 200,000 anesthetic procedures (2), which is close to our results for fulminant MH. This is not surprising because anesthetic practice in the United Kingdom appears similar to that in Denmark. Anesthetic practice as reported from Leeds (2) or Belfast (4), for example, does not seem to be very different from ours—with administration of succinylcholine in 40–45% of anesthetics and use of potent inhalation agents in 55–60%. In contrast to this low incidence, Britt and Kalow estimated that MH occurred in 1 of 14,000 anesthetics in Canada (1). However, their report is based upon data obtained before 1970, and since then an increasing awareness of MH has led anesthesiologists to terminate the anesthetic if early signs of MH develop, e.g., masseter spasm. This attitude would result in an increasing number of cases with mild symptoms of incipient MH; though masseter spasm may

**Table 4.** Total Number and Distribution of Suspected MH Cases during 6.5 yr

	Number of cases	Distribution of cases
Fulminant malignant hyperthermia	10	(6.5%)
Abortive malignant hyperthermia	144	
Masseter spasm + mild symptoms of MH		46 (29.9%)
Masseter spasm alone		47 (30.5%)
Mild symptoms of MH – masseter spasm		51 (33.1%)
Total	154	(100.0%)

The criteria applied in the classification of the patients are described in the text.

**Table 5.** Type of Anesthetic during which Suspected MH Occurred in 154 Probands

	Fulminant MH	Abortive MH
Potent inhalation agent + succinylcholine	8 (80%)	110 (76.4%)
Potent inhalation agent – succinylcholine	2 (20%)	17 (11.8%)
Intravenous anesthetic agents + succinylcholine	0 (0%)	17 (11.8%)
Total	10 (100%)	144 (100%)

also be due to unrelated diseases or even insufficient depth of anesthesia. The incidence of abortive MH or masseter spasm found in the present study is comparable to the incidence of MH reported by Britt and Kalow in 1970 in pediatric patients (1), and thus is in accordance with the above possibility.

As both incidence and mortality of MH vary depending on the criteria applied in the diagnosis, it can be argued that our data are not representative, because all cases of suspected MH reported to the register have been included in this study. However, it is not possible on clinical grounds to allow a definitive diagnosis of MH to be established if only a few symptoms of MH are present; and the patient therefore regarded and treated as MH-susceptible until proven MH-negative on muscle biopsy. The incidence of abortive MH reported here, accordingly, is not a "true" incidence of MH, but reflects the magnitude of the clinical problem. Earlier we found 50% of patients investigated because of masseter spasm to be MH-susceptible (3), and similar results have been reported by others (5–7). If this figure of 50% is applied to the present study, the incidence of "true" MH would be approximately half that presented in Table 6.

Unfortunately, no international classification of clinical MH exists, which makes comparison of different materials almost impossible. In this study, mortality from fulminant MH was 10%, which is considerably less than that found recently in a similar Scandinavian study (3) that included cases prior to 1978 (mortality 38%). The decrease in mortality probably reflects the increased attention paid in recent years to early signs of MH during anesthesia. As expected, abortive forms of MH were not associated

with any mortality. The male/female ratio found in this study was 1.4:1.0, which is in agreement with other reports (1–3). The age of the probands is similar in all the studies.

It is noteworthy that more than 75% of all reported MH cases in this study occurred during the combined use of a potent inhalation agent, usually halothane and succinylcholine (Table 5). In view of the many other side effects of succinylcholine it is interesting that this drug is still used in 45% of all anesthetics (Table 1). Perhaps the explanation is that the newer nondepolarizing muscle relaxants, with intermediate duration of action (e.g., vecuronium and atracurium), are not yet available for routine clinical use in Denmark. When these relaxants do become available, it may be prudent to reduce the use of succinylcholine and reserve this drug for emergency anesthesia where a rapid onset of paralysis is necessary.

One may expect the incidence of MH to decrease in the future as anesthetic practice continues to change. Fear of pollution may reduce the use of inhalation agents; new inhalation agents such as enflurane and isoflurane seem to be less likely to trigger MH than halothane (8). New neuromuscular relaxants have been developed that may reduce the use of succinylcholine; and a higher proportion of patients may well receive regional instead of general anesthesia. Nevertheless MH will still be encountered, especially in children, because inhalation anesthetics are often used during pediatric procedures.

In conclusion, fulminant MH was found to occur rarely (1:250,000 anesthetics), but suspicion of MH was raised in 1:16,000 of all types of anesthetics and in 1:4,200 anesthetics with the combined use of po-



Table 6. Incidence of Different Forms of MH in Relation to Type of Anesthesia

	Fulminant MH	Abortive MH (all subgroups included)	Overall incidence of suspected MH
Total number of anesthetics	1:251,063	1:17,435	1:16,303
General anesthesia	1:221,811	1:15,404	1:14,403
Anesthesia with potent inhalation agent	1:84,488	1:6,653	1:6,167
With succinylcholine	1:61,961	1:4,506	1:4,201
Without succinylcholine	1:174,597	1:20,541	1:18,379
Anesthesia with administration of succinylcholine	1:140,006	1:8,819	1:8,297

tent inhalation agents and succinylcholine. Masseter spasm occurred in 1:12,000 anesthetics in which succinylcholine was given.

My warmest thanks are extended to all Danish anesthesiologists and surgeons who helped with this investigation by answering the questionnaires. The Danish Malignant Hyperthermia Register has been supported by a grant from the Danish Medical Research Council.

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# A Retrospective Study of the Incidence and Causes of Failed Spinal Anesthetics in a University Hospital

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LEVY JH, ISLAS JA, GHIA JN, TURNBULL C. A retrospective study of the incidence and causes of failed spinal anesthetics in a university hospital. *Anesth Analg* 1985;64:705-10.

*One hundred sequential spinal anesthetic procedures were reviewed retrospectively to study specifically the incidence and causes of spinal anesthesia. Variables examined included the patient population, the technical aspects of performing subarachnoid tap and subsequent blockade, and the level of training of the anesthetists. We found a 17% incidence of spinal failure, defined as the need to use general anesthesia during the surgical procedure. Failure was found to be significantly associated with a lack of free flow of cerebral spinal fluid, the use of tetracaine without epinephrine, and an increased administration of intravenous supplementation. Forty-one% of the failures represented errors*

*in judgement, either in not properly anticipating the duration of surgery or injecting local anesthetic solution in the absence of a free flow of cerebral spinal fluid. An incidental finding was the lack of documentation in many of the variables examined. We attribute the high incidence of failed spinal anesthesia mainly to technical reasons, most of them avoidable. The use of local and regional anesthesia requires considerable technical skills and demands a precise and total understanding of regional anatomic relationships. With the decreasing use of regional anesthesia in our operating rooms, only those regional anesthesia techniques that require minimum dexterity, such as spinal and epidural anesthesia, continue to be utilized widely; and even these techniques, safe as they are, are being poorly taught.*

Key Words: ANESTHETIC TECHNIQUES—spinal.

Spinal anesthesia is a relatively easy technique to perform and provides excellent analgesia and relaxation with the use of a small amount of local anesthetic. However, complications, including hypotension, nausea, neurologic sequela, and death have been reported both during and after anesthesia (1). To add to this list of problems, we have experienced a number of failures after administration of spinal anesthesia in our University Hospital. As we were unable to find a study that dealt specifically with failure of spinal anesthesia in the literature, we studied one hundred spinal anesthetic procedures retrospectively to determine the apparent incidence and factors that correlate with failed block.

## Methods

One hundred consecutive spinal anesthetic procedures were selected from our file covering the period

from March 1982 to April 1983. If a patient received more than one spinal anesthetic, only the first was included in the study. Subsequent spinal anesthetics in that patient were then excluded from the study, i.e., each procedure was performed on a different individual. We analyzed the patient population with respect to age, sex, physical status, diagnosis, other medical problems (including lumbar spine abnormalities, coexisting neurological conditions, history of low back pain, previous laminectomy, history of spinal fusion, myelogram, discogram, neuropathy, or arachnoiditis), the planned surgical procedure, and whether or not the patient was given a premedication before the procedure. The variables involved in the spinal tap itself included the position of the patient (sitting, lateral, or prone), needle gauge, number of attempts required, reported presence or absence of a free flow of CSF, bloody CSF, paresthesias, and difficulty in entering the subarachnoid space. Anesthetic variables included the agent used, the amount injected, whether or not epinephrine was added, and the baricity of the solution. All tetracaine was commercially supplied as a 1.0% solution. In assessing the results of the anesthetic, we recorded the most cephalic dermatome affected, the duration of anesthesia, subjective patient complaints (e.g., nausea),

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Table 1. Demographic Factors

	Success	Failure	Total
Number of patients	83	17	100
Males	41	8	49
Females	42	9	51
Race			
White	51	11	62
Black	32	6	38
ASA physical status			
I	26	5	31
II	29	7	36
III	26	4	30
IV	2	1	3

objective complications (e.g., hypotension), supplemental agents required to maintain a hemodynamically stable intraoperative course, and supplemental drugs needed for patient comfort. Another factor examined was the level of training of the resident administering the anesthetic. We also recorded the name of the staff person who was supervising the resident because it was not necessarily recorded when attending assistance was required. All spinal anesthetic procedures known to be administered by attending physicians were performed only when they were specifically assigned to that case, i.e., no resident was involved. For the purposes of this study, we defined success as a spinal anesthetic that required no inhalational anesthetic agent to enable the surgeon to perform the given procedure while still maintaining a comfortable patient. If a patient required general anesthesia at any time during the surgical procedure, this was considered a failure. Pain and associated complaints persisting throughout the procedure, despite the frequent administration of narcotics or tranquilizers or both, were under suspicion but did not constitute failure for the purposes of this study.

Our statistical analyses were based on  $\chi^2$  tests, Fisher's exact tests, or *t*-tests. The *t*-tests were employed to analyze continuous variables; for example, did the average age of patients in whom there was spinal failure significantly differ from the age of patients in whom the spinal anesthetic was successful? The  $\chi^2$  or Fisher's tests were used to analyze categorical variables; for instance, was the presence or absence of a free flow of CSF significantly associated with spinal failure? Fisher's test was used when expected values were negligible. A 5% level of significance ( $P \leq 0.05$ ) was used to indicate statistical significance.

## Results

Spinal anesthesia failed in 17%, i.e., in 17 patients, spinal anesthesia was inadequate for completion of

Table 2. Type of Surgery

	Success	Failure
Intraabdominal		
Appendectomy	1	1
Hernia-abdominal	1	0
Tubal ligation	1	0
Cesarean section	0	2
Nonintraabdominal		
Transurethral resection	4	0
TUR and cystoscopy	10	1
Hernia inguinal	2	0
Lumbar laminectomy	1	0
Groin dissection—radical	1	0
Peripheral vascular	2	1
Hip replacement	2	1
Dilatation and curettage		
Radioactive implantation	17	2
Orchiectomy	0	1
Open bladder procedure	0	2
Vaginal procedures		
(hysterectomy, AP repair)	3	0
Perineal procedures	1	0
Lower extremity procedures	37	6
(amputation, vein stripping,		
arthroscopy, meniscectomy,		
open/closed reduction of fracture)		
Total	83	17

the surgical procedure and general anesthesia was required. Demographically (Table 1) there were 49 males and 51 females in our study. The age of the patients varied from 16 to 97 years (mean  $51.8 \pm$  SD 20.9); 62% were white, 38% black. Thirty-one patients were ASA physical status I, 36 were II, 30 were III, and 3 were IV. Duration of anesthesia varied from 25 to 300 min with a mean duration of 113.8 min ( $\pm$  SD 54.0). The types of operation for which spinal anesthesia was employed are summarized in Table 2. Pre-medication was used in 47% of the patients. All pre-medicants were administered 45 min to an hour before the procedure. Ten patients in our study had preexisting neurological conditions including hemiparesis, mental retardation, dementia, old cerebral vascular accidents, seizure disorders, diabetic neuropathy, and transient ischemic attacks. Fifteen patients had known lumbar spinal abnormalities as documented by radiographic studies. These included one patient with kyphosis, two with scoliosis, one with spondylolisthesis with degenerative joint disease, one with combined degenerative joint disease and metastatic disease, seven with only degenerative joint disease, two with previous spinal fusions, and one with fractured L4-5 vertebrae. None of these patients required general anesthesia.

Examination of the technical aspects showed that lumbar puncture was performed at the L3-4 inter-

Table 3. Technical Factors

	Success	Failure	Total
Needle Gauge			
25	41	6	47
22	36	10	46
20	1	0	1
Not recorded	5	1	6
Agent			
Tetracaine	64	14	78
Lidocaine	19	3	22
Tetracaine with epinephrine	29	2	31
Tetracaine alone	35	12 <sup>a</sup>	47
Lidocaine with epinephrine	1	2	3
Lidocaine alone	18	1	19
Amount (mg)			
Tetracaine	10.4	9.29	
Lidocaine	59.5	60.0	

<sup>a</sup> $\chi^2 = 4.70$ , d.f. = 1,  $P < 0.03$ .

space in 54 patients, at L2-3 in 18 patients, and at L4-5 in 17 patients. Five patients had lumbar punctures at multiple sites, including one patient who had lumbar puncture at L1-2; in five patients there was no mention of the site of lumbar puncture. Lumbar puncture was performed in the sitting position in 16 patients, and in the lateral position in 23 patients; in the remainder, position was not recorded. In seven patients, lumbar puncture was successful on the first attempt, and in 34 patients, two or more attempts at lumbar puncture were performed. In 59% of our sample these data were not recorded.

In 47 patients, lumbar puncture was done with a 25-gauge needle; and in 46 patients, a 22-gauge needle was used. In one patient a 20-gauge needle was used, and the needle gauge was not recorded in six patients (Table 3). Free flow of CSF was documented in 39 patients. A lack of free flow was documented in four patients. Whether flow was free or not was not recorded in 57 patients. CSF was tinged with blood in nine patients. There was no blood in CSF in 30 patients, and there was no documentation of the presence or absence of blood in 61 patients. Paresthesias were recorded in one patient, and in 19 patients there was a specific documentation of no paresthesias. Tetracaine was used in 78 patients, and lidocaine in 21 patients. All but one of the solutions used were hyperbaric. Epinephrine was used in 34 patients (Table 3). In none of the cases was general anesthesia begun prior to surgical stimulation or was spinal blockade reattempted.

In the hundred charts reviewed, sedative or analgesic supplementation or both was administered in 69% of the sample. The most commonly used drugs included diazepam, fentanyl, and thiopental. The most common subjective complaint noted during the

Table 4. Lack of Free Flow of CSF and Spinal Failure

	Success	Failure	Total
Free flow of CSF	33	6	39
No free flow of CSF	1	3	4
Total	34	9	43

Fisher's  $P < 0.03$ .

administration of subarachnoid block was nausea ( $n = 14$ ). Hypotension was by far the most commonly reported objective finding ( $n = 34$ ), followed by ECG changes (arrhythmias, ST segment changes) ( $n = 9$ ) and bradycardia ( $n = 4$ ). Two patients required frequent administration of narcotics and tranquilizers, but were not considered failures by our definition. The following factors were associated with spinal failure.

#### *Lack of Free Flow of CSF*

Although there was no documentation of the type of CSF flow in 57% of the patients, the available data showed significantly more spinal failures in patients in whom anesthesiologists failed to get a free flow of CSF (Fisher's  $P < 0.03$ ). Of the four anesthetic procedures in which free flow of CSF was not specifically mentioned, three resulted in failure (Table 4).

#### *The Use of Tetracaine Alone vs Tetracaine with Epinephrine*

Seventy-eight percent of the spinal anesthetics administered involved the use of tetracaine with or without epinephrine (Table 3). Fourteen of the 17 failures occurred with tetracaine. The use of tetracaine without epinephrine was involved in 12 of the 14 failures ( $\chi^2 = 4.70$ , d.f. = 1,  $P < 0.03$ ). These data can also be viewed from the following perspective: in only 6% (2 of 31) of the anesthetic procedures that involved tetracaine with epinephrine did the spinal anesthesia fail, whereas in 26% (12 of 47) of the anesthetic procedures in which tetracaine was used without epinephrine the spinal anesthetic failed.

#### *Increased Use of Intravenous Supplementation*

Ninety-four percent (16 of 17) of the patients in whom spinal anesthesia failed received intravenous supplementation, whereas 64% of patients with successful spinals required intravenous supplementation ( $\chi^2 = 6.04$ , d.f. = 1,  $P < 0.02$ ) (Table 5).

Variables that may merit further investigation in connection with spinal failure, although not statistically significant ( $0.05 < P < 0.25$ ) in the present study,



Table 5. Increased Intravenous Supplementation and Spinal Failure

	Success	Failure	Total
Supplemented	53	16	69
Not supplemented	30	1	31
Total	83	17	100

$$\chi^2 = 6.04, \text{ d.f.} = 1, P < 0.02.$$

include age, duration of surgical procedure, and use of diazepam premedication alone. The following variables were not significant with regard to spinal failure: sex, race, physical status, presence of preexisting neurologic conditions, level of spinal tap, position of patient for spinal tap, needle gauge used, presence of bloody CSF or paresthesia, difficulty in needle placement, level of anesthesia achieved, local anesthetic agent employed, and level of training of the person performing the spinal anesthetic.

## Discussion

From this study, it is evident that the incidence of failed spinals in our teaching institution is high. After a literature search, we could find only a few studies that alluded to spinal failure at all, and none were designed specifically to study the incidence of failure and the factors associated with failure. In his classic text, Lung (2) notes that "most articles dealing with spinal anesthesia make no reference to an inability to induce spinal anesthesia. Similarly, the incidence of inadequate spinal anesthesia reported is also very low."

In a recent article by Moore (3), a 16% incidence of failed spinal anesthesia was noted using a hyperbaric solution of tetracaine prepared by a pharmaceutical company. Although he acknowledges possible physician error, Moore alludes to the fact that the failure rate is higher than that noted using Niphanoid crystals of tetracaine. However, other studies (4,5) show that the success rate when premixed tetracaine is used, even when crystals are present in the solution, does not differ significantly from that achieved with Niphanoid crystals. It should be noted that in Moore's study, a spinal anesthetic was considered to have failed only if the surgery caused pain, and was considered successful if the surgical procedure exceeded the normal duration of local anesthetic used or if supplementation was needed for visceral pain. These criteria differ from ours and suggest that Moore's failure rate would have been higher had our more stringent criteria been chosen.

It is difficult to directly compare our rate of failure with the rate of failure in earlier studies (3,5-15) in that different local anesthetic agents were employed,

different surgical procedures were performed (especially in the early literature where higher levels of spinal anesthesia were much more frequently employed), and different practices with regard to supplementation were used. Furthermore, what constitutes failure of spinal anesthesia is rarely defined. Bearing this in mind, spinal failure rates range from a low of 0.46% (13) to a high of 16% (3), with most reports leaning toward the low end, i.e., less than 5%. It should be noted that four studies from the same institution found failure rates of 0.46% (13), 5% (5), 16% (3), and 10.6% (15). It was our purpose to examine what may have contributed to our high failure rate. Our study was limited because it was retrospective in nature; documentation in the anesthetic records examined was often lacking in what we consider the minimal information necessary when properly administering a spinal anesthetic; there may be factors associated with spinal failure equal to or more important than the ones we examined; surgical procedures were nonuniform; the decision to administer intravenous supplementation or general anesthesia or both to patients with spinal blockade was made on an individual basis, i.e., without specific indications; and only a small number of patient records were reviewed.

Despite these weaknesses, we were able to find several factors associated with spinal failures. Increased incidence of failure occurred when injection of local anesthetic was made in the absence of a free flow of CSF. The importance of a free flow of CSF was well known even in 1907, when Barker cautioned against injection of local anesthetic solution "unless the fluid [CSF] runs satisfactorily" (16).

Patients in whom tetracaine without epinephrine was used failed more often than patients who received tetracaine with epinephrine. This suggests that some of the spinal anesthetics failed due to judgement errors in anticipating the duration of surgery and thereby not using epinephrine in conjunction with the local anesthetic administered. Perhaps a continuous technique should be considered more often in potentially long operations. In addition, vasoconstrictors may in some way act to produce a more intense subarachnoid blockade through a variety of mechanisms, and in this manner their use may lower the incidence of spinal failure.

Also significant is the fact that the patients in whom spinal anesthesia ultimately failed according to our criteria required more intravenous supplementation during their spinal anesthetics than patients who did not fail, suggesting that general anesthesia was administered only after more conservative measures were tried. This also suggests varying degrees of failure,

i.e., some of the successful anesthetics may have been failures from the patients' perspective.

We do not know whether the high incidence of spinal failure in our present study is common, or if it is peculiar to teaching institutions, as there are no other similar recent studies available for nonteaching institutions for comparison. We would describe our staff as favoring general anesthesia (with a few exceptions), and feel that inadequate teaching or experience or both with regional anesthesia may have contributed significantly to our high failure rate. At least 41% (7 of 17) of the failures were due to errors in judgement, defined as not properly anticipating the length of surgery (four patients) and injection of local anesthetic solution in the absence of a free flow of CSF (three patients).

Our study shows no difference in the failure rates as the level of training of the anesthetist increases, and our failure rate is similar to that reported by an institution that favors regional anesthesia (3). Therefore, it is possible that spinal anesthesia has a high inherent failure rate that may be due to currently unknown technical factors. As noted by Allen in 1915, "failure may occur when every detail of the technic is carefully carried out and the injection is apparently successful. Many of these cases have been attributed to idiosyncrasy on the part of the patient, but this is hardly likely to be the case, except in a very limited number of patients, for if such frequent idiosyncrasies existed we would have more failure from local anesthesia. It is more likely due to some technical error. . . ." (5). For example, despite the many years spinal anesthesia has been practiced, selection of the proper dose of local anesthetic agent for a given procedure still remains an art. Larger prospective studies are necessary before these factors can be elucidated. As a first step towards clinical research, we recommend the following documentation for any regional technique: age of the patient; type, amount, and effect of premedication; the difficulty of performing the procedure; the history of paresthesias, accidental vascular puncture, or both; the anatomic site of needle entry; the type and amount of anesthetic agent used; the number of attempts; and the duration of the operation. For spinal anesthesia, documentation of a free flow of CSF is essential!

We believe that these present results are unacceptable if regional anesthesia is to maintain its viability among the many techniques available in our anesthetic armamentarium, especially when spinal anesthesia, probably the most commonly performed regional technique, is considered a barometer with regard to the practice of the rest of conduction anesthesia. All regional anesthesia requires a precise

knowledge of anatomy, physiology, and pharmacology, as well as a great deal of technical skill and bedside manner; facts that may not be appreciated by a large number of anesthesiologists. To improve the results of spinal anesthesia specifically and regional anesthesia in general, we believe it is necessary to increase the number of instructors with interest and expertise in this area and to promote the scientific aspects through research and teaching. In a recent article (17), Bridenbaugh concluded that because approximately 20% of surgical anesthetics were being administered with regional techniques in various teaching institutions, this apparently varied substantially from institution to institution, and that some anesthesia residency programs are indeed failing to teach regional anesthesia. In another article (18) addressing the same issue, Bridenbaugh noted that "a little regional anesthesia is being poorly taught and seldom encouraged in many teaching hospitals." Winnie noted that "instructors no longer have the expertise in regional techniques to allow them to teach residents properly" (19). Despite our high failure rate in the present study, we still endorse spinal anesthesia as a safe and effective technique, but realize that only through continued diligence in education will regional anesthesia flourish.

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## Vecuronium and *d*-Tubocurarine Combination: Potentiation of Effect

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MIRAKHUR RK, GIBSON FM, FERRES CJ. Vecuronium and *d*-tubocurarine combination: potentiation of effect. *Anesth Analg* 1985;64:711-4.

To evaluate possible potentiation of neuromuscular blocking effect of a combination of vecuronium and *d*-tubocurarine, cumulative dose-response curves were constructed to compare the potency of this combination with vecuronium and *d*-tubocurarine given alone. Ten patients each were given incremental injections of 80  $\mu\text{g/kg}$  *d*-tubocurarine or 5  $\mu\text{g/kg}$  vecuronium plus 40  $\mu\text{g/kg}$  *d*-tubocurarine, the data for incremental administration of 10  $\mu\text{g/kg}$  vecuronium being

used from our previously published study (7). The results showed the combination of vecuronium plus *d*-tubocurarine to be significantly more potent ( $P < 0.05$ ) than would be expected from a simple additive effect of the individual drugs given alone. The  $\text{ED}_{95}$  doses of *d*-tubocurarine and vecuronium were 530  $\mu\text{g/kg}$  and 57  $\mu\text{g/kg}$ , respectively, when administered alone, but when administered together, the  $\text{ED}_{95}$  doses were 160 and 20  $\mu\text{g/kg}$ , respectively.

**Key Words:** NEUROMUSCULAR RELAXANTS—*d*-tubocurarine, vecuronium. INTERACTIONS, DRUG—*d*-tubocurarine, vecuronium.

A combination of *d*-tubocurarine, or the structurally similar agent dimethyltubocurarine, with pancuronium has been shown to result in a greater than additive effect both in animal preparations and in humans (1-3). Vecuronium (4-6), a recently introduced monoquaternary analogue of pancuronium, has an additive but not potentiating effect when administered with pancuronium (7). Preliminary in vitro studies (phrenic nerve-hemidiaphragm preparations) have shown potentiation of the neuromuscular blocking effect of vecuronium, following prior administration of *d*-tubocurarine and dimethyltubocurarine in doses which themselves were associated with a block of less than 10% (8). In this study, we have investigated the neuromuscular blocking effects of *d*-tubocurarine and a *d*-tubocurarine-vecuronium mixture in anesthetized humans, and compared the results with our previously published study with vecuronium using similar methods (7).

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## Methods

Adult ASA class I patients scheduled for elective ophthalmic surgery were studied. Informed consent was obtained from all the patients and the study was approved by the local Hospital and University Ethical Committee. Premedication was given with diazepam, 10-15 mg, orally about an hour preoperatively. Anesthesia was induced with thiopental and maintained with 70%  $\text{N}_2\text{O}$  in oxygen and intravenous fentanyl, with additional thiopental as required. Ventilation was assisted as necessary to maintain end-tidal carbon dioxide at approximately 5%. Heart rate was continuously monitored on an oscilloscope and blood pressure measured and recorded using an oscillotonometer (Dinamap, Critikon Ltd).

After induction of anesthesia the ulnar nerve was stimulated at the wrist with supramaximal square wave pulses of 0.2-msec duration at 0.1 Hz via percutaneous electrodes using a peripheral nerve stimulator (Myotest, Biometer Ltd). The resultant force of thumb adduction was measured and recorded using a transducer and a neuromuscular function analyzer (Myograph 2000, Biometer Ltd) (9). The control twitch height was allowed to stabilize for at least 10 min. The patients were then randomly allocated to receive increments of either 80  $\mu\text{g/kg}$  *d*-tubocurarine or a combination of 5  $\mu\text{g/kg}$  vecuronium and 40  $\mu\text{g/kg}$  *d*-tubocurarine. Further increments of relaxant or the combination were administered when the twitch

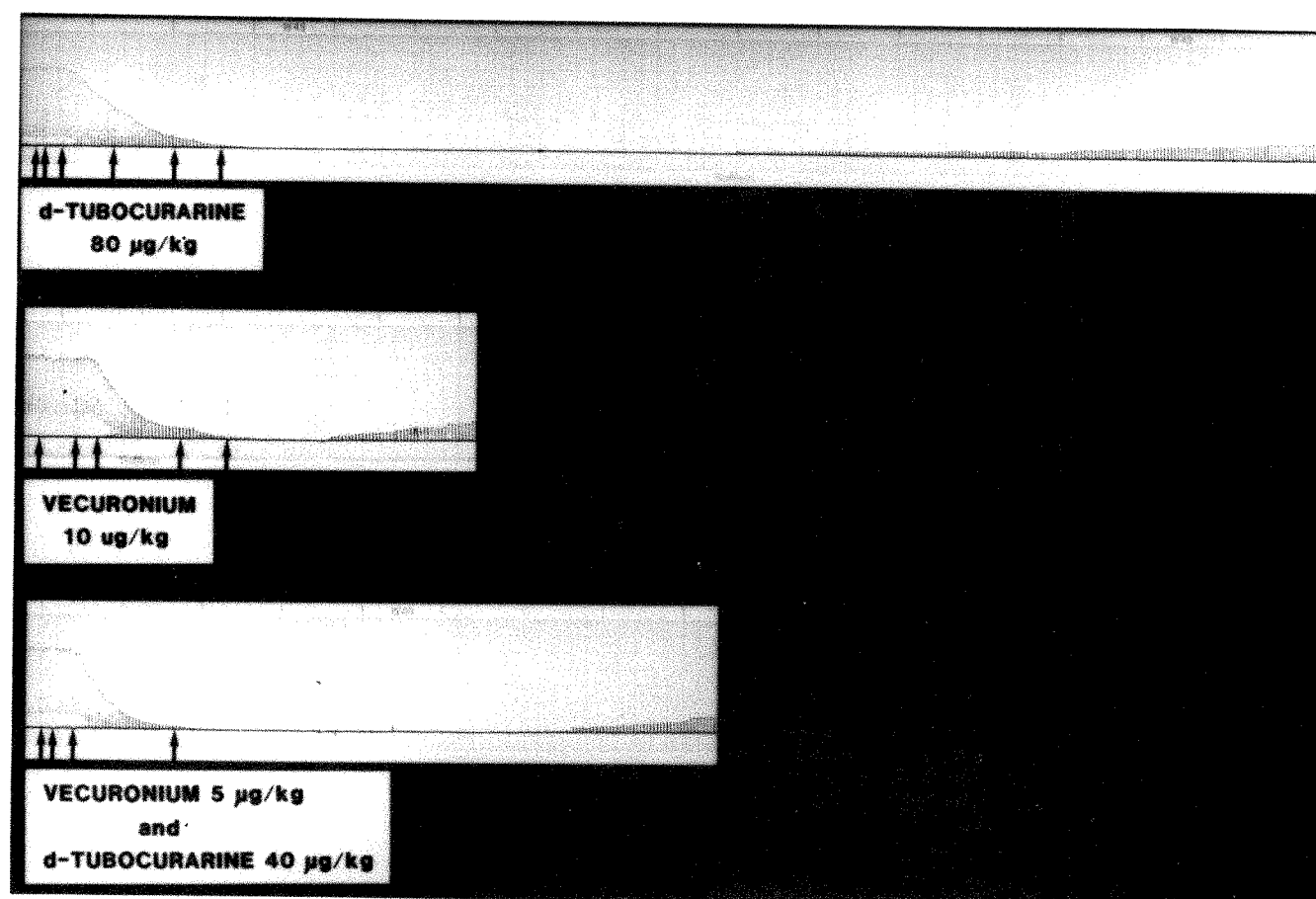


Figure 1. Representative recordings of the administration of *d*-tubocurarine, vecuronium, and their combination. Further increments were administered at the arrows. The end of the recording corresponds to 25% recovery of twitch height. Data for vecuronium from Ferres et al. (7).

height was the same in response to three consecutive stimuli at 0.1 Hz until 95% block of the twitch response was achieved (Fig. 1). In our previous study (7), vecuronium was given in increments of 10 µg/kg to the same end point. The study was terminated at this stage and anesthesia continued as appropriate for surgery.

An arc-sine transformation of the data relating to the twitch height was carried out according to Armitage (10), for the response involving the two extreme (0 and 100%) points on the dose-response curves. Linear regression analysis of these data was carried out to plot the cumulative dose-response curves. The number of increments of *d*-tubocurarine or the combination required for 95% depression of the twitch height was calculated. The statistical significance of the data was ascertained using analysis of variance and *t*-tests.

Table 1. Patient Characteristics

	Age (yr)	Weight (kg)
<i>d</i> -Tubocurarine	36 ± 5.4	62 ± 3.1
Vecuronium*	33 ± 5.3	59 ± 4.0
Combination	28 ± 4.2	60 ± 6.6

Values are given as mean ± SEM.

\*From Ferres et al. (7).

## Results

The ten patients studied in each of the two groups were similar to each other as well as to those in our previous study of vecuronium (7) with regard to physical characteristics (Table 1). Dose-response curves for *d*-tubocurarine, vecuronium, and the combination are shown in Figure 2, and their correlation coefficients, slopes, and intercepts in Table 2. The dose-response curve for the combination is to the left of the dose-response curves for the individual relaxants. Analysis of variance showed a significant difference ( $f = 7.87$ ,  $P < 0.01$ ) in the slopes of the lines among the three groups. Further analysis using a *t*-test showed the dose-response curves for vecuron-



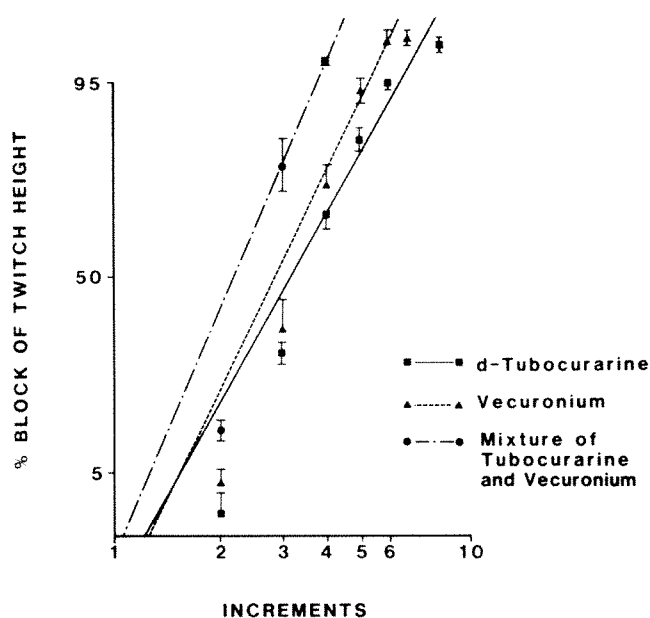


Figure 2. Dose-response curves for *d*-tubocurarine ■—■, vecuronium ▲—▲, and their combination ●—●. Each point represents mean  $\pm$  SEM. Data for vecuronium from Ferres et al. (7). Slope-intercept equations: arcsine of response =  $-10.51 + 109.54 \log$  number of increments for *d*-tubocurarine;  $-12.85 + 126.66 \log$  number of increments for vecuronium;  $-3.69 + 143.00 \log$  number of increments for the combination.

Table 2. Data on Regression Analysis

	<i>d</i> -Tubocurarine	Vecuronium	<i>d</i> -Tubocurarine- vecuronium combination
Correlation coefficient ( <i>r</i> )	0.90	0.92	0.90
Slope $\pm$ SEM	109.6 $\pm$ 4.51	126.7 $\pm$ 6.98	143.0 $\pm$ 7.00
Intercept (number of increments)	1.295	1.255	1.097

ium and the mixture did not differ significantly in their slopes, but the slope of the dose-response curve for *d*-tubocurarine differed from the slopes of the curves for vecuronium and the mixture. There was a significant difference in the intercepts on the x-axis among the three groups using the analysis of variance ( $f = 5.47$ ,  $P < 0.01$ ). A *t*-test showed no difference between the intercepts of *d*-tubocurarine and vecuronium, but both were significantly different ( $P < 0.01$ ) from that of the combination—showing its greater potency.

The number of increments required to produce a 50 and 95% depression of twitch height ( $ED_{50}$  and  $ED_{95}$ ) is shown in Table 3. Analysis of variance showed a significant difference in these between the groups ( $f = 6.16$  for  $ED_{50}$ , and  $5.80$  for  $ED_{95}$ ;  $P < 0.01$  for both). There is, however, no significant difference in

Table 3. Number of Increments Required to Produce 50 and 95% Block and the  $ED_{95}$  Doses of Individual Relaxants and Their Combination

	$ED_{50}$ (number of increments)	$ED_{95}$ (number of increments)	$ED_{95}$ ( $\mu$ g/kg)
<i>d</i> -Tubocurarine	3.30 (2.90–3.69)	6.62 (5.46–7.77)	530
Vecuronium <sup>a</sup>	3.05 (2.44–3.67)	5.67 (4.10–7.25)	57
<i>d</i> -Tubocurarine plus vecuronium	2.33 <sup>b</sup> (2.01–2.64)	4.02 <sup>b</sup> (3.13–4.91)	160 +

Figures in parenthesis represent 95% confidence limits.

<sup>a</sup>From Ferres et al. (7).

<sup>b</sup>Significantly different from *d*-tubocurarine and vecuronium for both end-points.

these between *d*-tubocurarine and vecuronium using the *t*-test, but significantly fewer increments ( $P < 0.05$ ) are required for both  $ED_{50}$  and  $ED_{95}$  end points with the combination when compared with either relaxant individually. Table 3 also shows that  $ED_{50}$  is  $57 \mu$ g/kg for vecuronium,  $530 \mu$ g/kg for *d*-tubocurarine, and  $20 \mu$ g/kg and  $160 \mu$ g/kg for vecuronium and *d*-tubocurarine, respectively, when used together.

## Discussion

The observed potentiation of neuromuscular blockade associated with a combination of vecuronium and *d*-tubocurarine in humans in the present study confirms similar observations made earlier in animal studies (8). Such potentiation has been observed previously when pancuronium, which is structurally similar to vecuronium, is given in combination with *d*-tubocurarine (1,3).

Although the mechanisms of such potentiation are not clearly defined, it is likely that they are similar for both pancuronium and vecuronium, when administered with *d*-tubocurarine. Differences in protein binding as a cause of the potentiation have been discounted (11). Alterations in tissue blood flow have also been shown not to be responsible for this potentiation (12). A more plausible reason for the potentiation may be the action of these two drugs occurring at more than one site to different degrees. Possibly a prejunctional action to impair transmitter release occurs, as well as the more familiar postjunctional receptor block. A greater than additive effect would occur if the two drugs acted at two sites to relatively different degrees. Such a prejunctional effect has been shown with *d*-tubocurarine (13–15), although only at higher frequencies of stimulation. More recently, however, differential prejunctional and postjunc-

tional effects with different relaxants have also been demonstrated using a train-of-four stimulation every 12 sec (16). According to Foldes et al. (8), the decreased acetylcholine release due to *d*-tubocurarine would increase the potency of drugs such as vecuronium that may act mainly at postjunctional receptors. Pharmacokinetic factors such as one drug affecting the distribution ( $t_a$ ) of the other could perhaps be responsible. However, there is no direct evidence to support such a hypothesis at the present time.

The use of a cumulative dose-response technique for studies of relaxants with intermediate duration of action such as vecuronium may be questioned, particularly when compared to longer acting agents like *d*-tubocurarine. However, no potentiation of pancuronium occurs when vecuronium is combined with pancuronium, an agent with a duration of action similar to *d*-tubocurarine, using the same methods (7).

Investigations of neuromuscular blocking effects of many combinations of nondepolarizing relaxants have been reported—e.g., gallamine and *d*-tubocurarine (12,17), pancuronium and *d*-tubocurarine or metocurine (1), pancuronium and alcuronium (3,18), vecuronium and pancuronium (7)—but potentiation has been shown to occur only when *d*-tubocurarine or metocurine has been one of the components of the mixture.

A practical advantage of using a combination of pancuronium with *d*-tubocurarine or dimethyltubocurarine is hemodynamic stability, shorter duration of clinical relaxation, and a slightly faster onset of action in the case of pancuronium-*d*-tubocurarine mixture (2,19). All these considerations may not apply as much in the case of *d*-tubocurarine-vecuronium mixtures, because vecuronium by itself is associated with a relatively shorter duration of action and considerable hemodynamic stability (6,20-22). However, the onset of action may be improved and this aspect is worth investigation.

In conclusion, the present study shows potentiation of neuromuscular blockade when vecuronium and *d*-tubocurarine are administered together.

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## Review Article

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# Distribution of Local Anesthetic Solutions within the Subarachnoid Space

Nicholas M. Greene, MD

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Uptake of local anesthetics injected into the subarachnoid space determines which neuronal functions are affected during spinal anesthesia. Elimination of local anesthetics from the subarachnoid space determines the duration of these effects. Distribution of local anesthetics within cerebrospinal fluid (CSF) determines the extent of altered neuronal function. Uptake and elimination have been reviewed previously (1). The present review deals with distribution, the determinant of the level of spinal anesthesia.

Studies of drug distribution usually rest upon measurements of concentrations of the drug as a function of time after administration. Technical and ethical considerations make it impossible to take multiple samples of CSF at different levels of the subarachnoid space in patients. Reliance must, therefore, be placed upon estimates of distribution of local anesthetics in CSF not by measuring drug concentrations in CSF but, instead, by measuring the extent of neurologic responses to local anesthetics in CSF. The neurologic response that will be relied upon in this review, for estimation of local anesthetic distribution in CSF, is the spinal segmental level of anesthesia. Anesthesia is defined (for the present purposes only) as loss of pinprick sensation. This definition of anesthesia is employed because it is the definition most widely used by clinicians in determining the level to which local anesthetic solutions have spread. Differences between the levels of anesthesia as thus defined and levels of analgesia, somatic motor paralysis, sympathetic denervation, and other forms of neuronal impairment are not dwelt upon. These other forms of

neuronal impairment during spinal anesthesia reflect differences in uptake by different neuronal tissues and differences in sensitivity of various nerve tissues to the effects of local anesthetics. They are neurophysiologically and clinically important, but they are basically irrelevant to the question addressed in this review: the factors that determine distribution of local anesthetic solutions in CSF.

In using anesthesia as defined above as an index of distribution of local anesthetics in CSF, it should be noted that many of the studies on spinal anesthesia that will be cited, especially those from Britain, make a clear and, given the purpose of these studies, important distinction between levels of anesthesia and levels of analgesia. These studies usually define analgesia as inability to appreciate pinprick, and anesthesia as the inability to appreciate touch (see Brown et al. (2)). The difference in definition of anesthesia, as used in these citations and as used in this review, should be borne in mind when the present text cites the levels of anesthesia reported in the British studies.

Only the distribution of local anesthetic solutions in CSF will be considered. The distribution of intrathecally administered opioids in CSF, a different subject, will not be considered. Furthermore, the review is limited primarily to anesthetic solutions that not only are approved for spinal anesthesia in the US but also enjoy widespread clinical use.

Finally, distribution is considered in terms of levels of anesthesia after establishment of a pharmacologic steady state. Maximum levels of anesthesia are used as an index of maximum spread in CSF. Time to onset of anesthesia and time required to achieve maximum levels are not considered.

Twenty-five factors have been invoked as determinants of the spread of local anesthetic solutions in CSF (Table 1). Some are hypothetical; though often cited, many of the hypothetical factors have not been

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**Table 1.** Factors Influencing Distribution of Local Anesthetic Solutions in Cerebrospinal Fluid<sup>a</sup>

Patient characteristics
Age
Height
Weight
Gender
Intraabdominal pressure
Anatomic configuration of spinal column
Position
Technique of injection
Site of injection
Direction of injection
Direction of needle
Direction of bevel
Turbulence
Rate of injection
Barbotage
Diffusion
Characteristics of spinal fluid
Composition
Circulation
Volume
Pressure
Density
Characteristics of anesthetic solution
Density
Definitions
Density
Specific gravity
Baricity
Hypobaric solutions
Isobaric solutions
Hyperbaric solutions
Amount of anesthetic
Concentration of anesthetic
Volume injected
Isobaric solutions
Hypobaric solutions
Hyperbaric solutions
Vasoconstrictors

<sup>a</sup>Hypothetical or demonstrable.

proven to be significant determinants of distribution of spinal anesthetic solutions. Others are of demonstrable clinical importance in determining the extent to which a local anesthetic is distributed after injection into the subarachnoid space.

Given the multitude of factors that either actually do influence, or are said to influence, distribution of local anesthetic solutions in CSF, it is necessary, if the role of one of the 25 factors is to be accurately quantitated, that the remaining 24 factors be kept constant. This may often be difficult to accomplish under clinical conditions. Lack of suitable control of all variables that might possibly affect distribution may not negate the clinical value of such studies, but it may negate their value in proving the clinical significance of various factors that determine distribution of local an-

esthetic solutions used for spinal anesthesia. Studies that, in the opinion of the author, fail to provide appropriate control of experimental conditions are therefore not cited.

Finally, the purpose of this review is to derive and define determinants of the spread of spinal anesthetics that are clinically meaningful in everyday practice. The studies cited deal thus almost exclusively with observations made in humans, almost always under clinical conditions. Differences between humans and animals are, in the case of distribution of spinal anesthetic solutions in CSF, so great as to preclude application to humans of data obtained in animals.

## Patient Characteristics

### Age

Nightingale mentions, in a clinical study directed principally to evaluation of the effect of barbotage on the level of anesthesia, that age had no effect on the level of 0.5% dextrose-free bupivacaine spinal anesthesia (3). Data that would allow statistical analysis of the effects of age on distribution are, however, not presented. Also, the 67 patients studied ranged in age from 62 to 90 (mean 74.1 years). Lack of a suitable number of middle-aged or younger patients makes it difficult to assess the effect of age on spread of spinal anesthetic solutions in this study. Cameron et al., on the other hand, studied 33 patients aged 37-97 specifically to determine the effect of age on distribution of spinal anesthetic solutions (4). All patients were given 4.0 ml 0.5% dextrose-free bupivacaine injected intrathecally at L3-4 at a rate of 0.5 ml/sec through a 22-g needle. The authors found a small but statistically significant ( $P < 0.05$ ) correlation between age and level of anesthesia. The greater the age, the more cephalad the level of anesthesia. Pitkänen and associates came to the same conclusion (5). They divided their patients by decades: aged 15-19 ( $n = 6$ ), 20-29 ( $n = 23$ ), 30-39 ( $n = 24$ ), 40-49 ( $n = 14$ ), 50-59 ( $n = 21$ ), 60-69 ( $n = 16$ ), 70-79 ( $n = 10$ ), and 80 and older ( $n = 11$ ). All patients were given 3.0 ml 0.5% dextrose-free bupivacaine. They, too, found a small but statistically significant ( $P < 0.05$ ) correlation between age and cephalad spread of anesthesia. The difference in level of anesthesia was not significant from one decade of life to the next. The gradual, but steady, increase in level of anesthesia throughout eight decades did, nevertheless, result in statistically significant differences in levels of anesthesia in the younger and in the older decades of life. Though statistically significant, the correlation between age and spread was, as



the authors noted, weak, and the age-related differences in spread were so small as to be of marginal clinical significance. The maximum spread of anesthesia averaged T9 in patients 20–28 years old, T7 in patients aged 70–79 and T6 in patients 80 years old and older. The data of Pitkänen et al. and Cameron et al. suggest that the tendency to an increase in spread with age, also observed by Bengtsson et al. (6), may well be more than just a tendency.

The data of Pitkänen and Cameron and their associates demonstrate that increasing age is associated with a small, but statistically significant, increase in level of anesthesia of perhaps modest clinical significance when an essentially isobaric solution of 0.5% bupivacaine is injected. Comparable well controlled data on the spread of hypo- and hyperbaric spinal anesthetic solutions are not available. Nor can they necessarily be inferred from data derived from studies in which an isobaric solution is used. Such an inference would be unwarranted in the absence of an explanation as to why spread of isobaric solutions in CSF is a direct function of age. No data on the effect of age on volume of spinal CSF are available. If, however, age were associated with progressive decrease in CSF volume, this might mean, because volume of CSF is, as amplified below, a determinant of spread of hyperbaric solutions, that the data of Pitkänen et al. and Cameron et al. could also be applied to situations in which hyperbaric solution are used. However, this requires further studies.

### *Height*

There have been no controlled, systematic studies of the effect of patient height on distribution of spinal anesthetic solutions. Common sense and clinical experience tell us, nevertheless, that injection of a local anesthetic solution at the L3–4 interspace in a short patient is associated with a more cephalad spinal segmental level of anesthesia than is injection of the same amount of the same anesthetic injected in the same way in a tall patient. One reason for this is that even if the anesthetic solution were to spread to an equal extent, 20 cm, say, from the site of injection in both the tall and the short patient, a 20-cm spread will reach a higher spinal segmental level in the short patient than it will in the tall patient.

An additional reason for lower segmental levels of anesthesia in taller patients than in shorter patients is that the local anesthetic solution that spreads 20 cm from the site of injection in a short patient may not spread the same distance, 20 cm, in a tall patient. It may not spread as far in the tall patient because of height-related differences in spinal CSF volume. The

volume of CSF below the termination of the cord at L2 is greater in tall than in short subjects because the length of the cauda equina is greater. The initial volume of CSF into which the local anesthetic is injected at L3–4 being greater, there will be greater dilution of the anesthetic solution at the site of injection and therefore less cephalad spread in the taller patient. The volume of CSF above termination of the cord at L2 may also be greater in tall patients than in short patients. The diameter of the spinal cord is greater in taller patients than in shorter patients. So, too, is the depth of the subarachnoid space, i.e., distance from dura to pia mater. Although the ratio between depth of the subarachnoid space and diameter of the cord remains constant regardless of height, there is, however, a slight increase in absolute volume of CSF at any given level of the cord due to the increase in depth of the subarachnoid space. The increase in volume of CSF above L2 in taller patients would further dilute local anesthetic solutions injected at L3–4 and so be a contributory factor to the lower levels of anesthesia observed in taller patients.

Differences in height must be fairly substantial if they are to have clinically significant effects on distribution of spinal anesthetic solutions. Men are, on the average, taller than women. The difference is not great enough, however, to result in sex-related differences in levels of anesthesia when identical anesthetic techniques are used in both sexes (2). But distribution is certainly different in patients 210 cm tall than it is in patients 120 cm tall. The role of patient height in determining sensory levels of anesthesia becomes clinically most important when spinal anesthesia is used in children.

### *Weight*

How much a patient weighs has no effect on distribution of local anesthetic solutions in CSF. The spread of a spinal anesthetic solution is the same in a 70 kg patient as it is in a patient weighing 100 kg when all other factors determining spread, including height, are constant. The theoretical possibility that obesity may be associated with an accumulation of epidural fat sufficient to reduce the volume of CSF and, therefore, alter distribution of local anesthetic solutions in the subarachnoid space has not been rigorously studied. Clinical experience indicates that obesity is of little, if any, direct clinical significance in determining spread of local anesthetic solutions in CSF.

Obesity may, however, indirectly affect spread of a spinal anesthetic solution that is normally governed by gravity. A hyperbaric solution may, for example, be associated with unexpectedly great cephalad spread

in a steatopygous patient. Such a patient will be in the slight head-down position even though lying supine on an operating table that is horizontal.

### *Gender*

The sex of a patient has no direct effect on distribution of local anesthetic solutions in CSF if all other factors involved in determining distribution are constant (2). From a practical point of view it should, however, be borne in mind that in women the width of the hips is usually greater than the width of the shoulders. A woman may thus be slightly head-down when in the lateral position on an operating table that is horizontal with the floor. This will particularly affect distribution of hyperbaric solutions. Men, having shoulders that are usually wider than their hips, will be in the slight head-up position under the same conditions.

### *Intraabdominal Pressure*

An increase in intraabdominal pressure may be, and often is, associated with an increase in spread of local anesthetic solutions in the subarachnoid space. This is because increased intraabdominal pressure causes obstruction of vascular channels that normally account for venous drainage from the abdomen. The result is dilation of collateral venous channels from the abdomen, including venous channels that pass through the lower portions of the epidural space. Epidural venodilation in turn reduces the volume of CSF in the lumbar subarachnoid space, and thus the volume of CSF in the lumbar and lower thoracic subarachnoid space. The effect of decreases in volume of spinal CSF on distribution of spinal anesthetic solutions is dealt with further below (CSF Volume section), but it should be noted that chronic increases in intraabdominal pressure have more effect on altering distribution of spinal anesthetic solutions than do acute increases in intraabdominal pressure. The effects are clinically most evident in term pregnancies and in patients with ascites or large intraabdominal tumors.

### *Anatomic Configuration of the Spinal Column*

Scoliosis has no significant effect on the distribution of spinal anesthetic solutions. Kyphosis, flattening of the lumbar lordotic curvature (as with flexion of the thighs on the abdomen in the supine position), and accentuation of the lordotic curvature (as in term pregnancy) may all significantly affect distribution of spinal anesthetic solutions the spread of which is governed by gravity. They do so because they either accentuate or eliminate the lower portion of the S-shaped curve

of the subarachnoid space normally present when a patient lies in the supine position. Elimination of the lordotic curve increases the cephalad spread of hyperbaric solutions (7). Exaggeration of the lordotic curve may decrease the cephalad spread of hyperbaric solutions in the supine position by causing pooling of the anesthetic solution in the deepest part of the S-shaped curve. Kyphotic accentuation of the thoracic curvature similarly affects thoracic distribution of local anesthetic solutions the spread of which is determined by gravity. An increase in anterior-posterior thoracic diameter, as seen with emphysema, may result in a kyphotic-like condition such that the upper thoracic spine may be in the slight head-up position when an emphysematous patient lies supine on an operating table in the horizontal position.

### *Position*

Position of the patient and baricity or density of the local anesthetic solution injected as determinants of distribution are so closely related that one cannot be discussed without the other. The roles of both are considered below in the section that deals with the effect of density on distribution.

## **Technique of Injection**

Where and how a local anesthetic solution is injected into the subarachnoid space may affect its distribution within the subarachnoid space.

### *Site of Injection*

Injection of a local anesthetic solution into the subarachnoid space cephalad to the L2-3 interspace causes, of course, a shift in the cephalad direction of the epicenter from which subsequent distribution of the anesthetic solution takes place. If injected at the T6-7 level, the nerve roots primarily affected will be thoracic roots instead of lumbar roots, as with more conventional spinal anesthetics. But injection above L2 does more than alter the epicenter of spinal anesthesia. It also alters distribution of the anesthetic solution in CSF. It does so because the volume of CSF per spinal cord segment is less above L2 than below L2. It is less because the spinal cord ends (in adults) at L2. Above L2 the spinal cord occupies a substantial portion of the subarachnoid space with consequent reduction in volume of CSF. Accordingly, injection of, say, 2 ml of anesthetic solution at T6-7 is associated with a greater spread than if the same volume of anesthetic solution were injected into the greater volume of CSF at the L3-4 interspace. Denervations

would accordingly be more extensive and involve more nerve roots in the thoracic area than in the lumbar area.

Spinal anesthesia is, of course, rarely if ever intentionally induced by injecting local anesthetic solutions above the L2-3 interspace. The proximity of the cord to the dura above L2, and the resulting shallowness of the subarachnoid space, increase the risk of trauma to the cord by the spinal needle. Spinal anesthetics resulting from injections made above L2 are usually complications associated either with nerve blocks in the cervical or posterior thoracic area, or with thoracic or cervical epidural anesthesia. If the dura is accidentally penetrated during such procedures, even though the volume of local anesthetic going into the subarachnoid space is little, the resulting area of denervation will be unexpectedly great.

### *Direction of Injection*

*Direction of needle.* Though unquantitated, it appears likely that the direction of the needle at the time the spinal anesthetic solution is injected—that is, the angle between the needle and the longitudinal axis of the subarachnoid space—may influence the direction in which the local anesthetic goes after injection. If the needle is directed in a cephalad direction, the stream of anesthetic solution coming from the needle during injection would be expected to carry the anesthetic solution farther in a cephalad direction than if the same anesthetic solution were injected through a needle inserted through the dura at a right angle to the long axis of the spinal column. When injected through a needle at a right angle to the spinal column, the initial distribution of anesthetic solution in CSF is essentially equal above and below the site of injection. The initial distribution in CSF of anesthetic injected through a needle pointing in the cephalad direction would be likely to be greater above the site of injection than below it.

*Direction of bevel.* The direction in which the bevel of a standard lumbar puncture needle faces has no effect on the distribution of local anesthetic solutions in CSF (8). The lumen of a standard lumbar puncture needle lies in the same axis as the lumen of the shaft of the needle. There is no bend or angulation of the terminal lumen at the bevel. A liquid injected through such a needle exits from the needle in the same straight line formed by the lumen of the needle throughout its length. When a solution is injected into air through a standard beveled lumbar puncture needle, the exit stream goes in the same straight line regardless of the direction in which the bevel faces.

There are, however, lumbar puncture needles specifically designed to influence the direction in which an injected solution exits from the needle. One of these is the Whitacre needle. The Whitacre needle has a closed, pencil-point tip with a lateral exit port immediately adjacent to the start of the angle forming the pointed tip. Another is the Tuohy needle. The tip of a Tuohy needle has a sharp but closed bevel; the lumen of the needle is curved at the distal end so that the exit port lies on the extreme tip of the shaft at the start of the angle of the bevel. Both these needles determine the angle at which fluids leave the lumen. With the Whitacre needle, the exit stream is essentially at a 90° angle to the shaft of the needle. With the Tuohy needle, the exit stream is at a 45° angle. Both significantly affect the direction in which anesthetic solutions are injected into CSF. Thus both affect distribution of spinal anesthetic solutions.

### *Turbulence*

*Rate and force of injection.* Turbulence inevitably occurs in CSF when solutions are injected into the subarachnoid space. If turbulence has a clinically significant effect on spread of spinal anesthetic solutions within the subarachnoid space, then the force used for injection should increase the level of spinal anesthesia. Neigh et al. found, however, that the level of sensory anesthesia was the same in patients in whom a hyperbaric solution of tetracaine was injected at a rate of 1 ml/sec as it was in patients in whom the same volume of anesthetic solution was injected through the same size needle at a rate of 0.2 ml/sec (8). Similarly, McClure et al. found that the injection of 4 ml of isobaric tetracaine at a rate of 0.2 ml/sec through a 25-g needle resulted in essentially similar levels of anesthesia as did injection of 4 ml of the same solution through the same size needle at a rate of 0.1 ml/sec (9).

The studies of Neigh and of McClure and their associates indicate that turbulence created within the subarachnoid space, when the force or rate of injection was altered, has no clinically significant effect on the spread of spinal anesthetic solutions in CSF. Perhaps, however, differences in the amount of turbulence created by varying the rate of injection through needles of the same size, as in these clinical studies, were not great enough to produce clinically meaningful changes in the spread of the anesthetic solutions used.

*Barbotage.* What happens when even greater degrees of turbulence are deliberately produced by barbotage, that is, aspiration of CSF and anesthetic so-

lution just injected back into the syringe used for injection immediately upon completion of injection, followed by reinjection into CSF of the contents of the syringe? The volume of fluid aspirated back into the syringe may be less than, equal to, or greater than the volume of the initial injectate. Aspiration and reinjection may be done one or more times.

Kitahara et al., evaluating the spread of local anesthetic solutions in patients by measuring the distribution of a small amount of radioactive iodine added to the anesthetic solution (10), found that barbotage (the details of the barbotage technique were not described) in an unstated number of patients had no effect on the spread of isobaric solutions of dibucaine or tetracaine. Lanz et al. also found that, in a constant temperature model of the subarachnoid space, vigorous barbotage had no significant effect on distribution of isobaric solutions of bupivacaine, lidocaine, mepivacaine, prilocaine, or tetracaine (11). In a well-controlled clinical study, Levin et al. found that barbotage (aspiration of the injected volume back into the syringe followed by reinjection 2-4 times with 0.5 ml increases in each aspirated volume) had no significant effect on the spread of either iso- or hyperbaric solutions of tetracaine (12). Nightingale, in a similar clinical study of isobaric bupivacaine spinal anesthesia with ( $n = 31$ ) or without ( $n = 36$ ) barbotage (half the initial injected volume aspirated and reinjected followed by a second aspiration and reinjection of one quarter the initial injected volume), also found that barbotage had no effect on the level of anesthesia (3).

Though there are no clinical studies of the effect of barbotage on distribution of hypobaric solutions, the above studies show that turbulence, no matter how produced, has no clinically significant effect on distribution of hyper- and isobaric spinal anesthetic solutions. There is no a priori reason why those findings cannot be applied to hypobaric solutions.

How can the above objective data be reconciled with the intuitively reasonable hypothesis that turbulence at the site of injection increases the spread of spinal anesthetic solutions? The most likely explanation is that the turbulence is not only relatively brief in duration, but is also restricted to the area at, and immediately adjacent to, the site of injection. To alter distribution to any significant degree, turbulence should last for more than moments. It should also extend well beyond the site of injection. Neither seems likely. Transient turbulence localized about the L3-4 interspace will hardly affect spread of a solution of any baricity 20 cm away from the site of injection. On the other hand, local turbulence at the site of injection will thwart attempts to limit the cephalad level of

anesthesia to L2 or L3 as well as attempts to induce totally unilateral low spinal anesthesia.

## Diffusion

Diffusion, a term often loosely applied to spinal anesthesia, is of no importance in determining distribution of spinal anesthetic solutions under clinical conditions. True physical diffusion consists of the intermingling of different types of molecules uninfluenced by turbulence or differences in density. It is a slow process, requiring hours to cover a distance of centimeters. Distribution of local anesthetic solutions in CSF is completed in minutes, not hours.

## Characteristics of CSF

Determinants of the spread of one solution in another solution include the physical characteristics of each of the solutions. The physical characteristics of CSF are thus one of the factors governing distribution of local anesthetic solutions in CSF.

### *Composition of CSF*

The normal range of values of CSF pH and CSF concentrations of cells, protein, glucose, and ions is too narrow to have any effect on distribution of spinal anesthetic solutions (13). Values beyond the normal range may affect distribution, but they are associated only with neurologic conditions that contraindicate spinal anesthesia in the first place.

The concentration of protein in CSF increases progressively with descent from the ventricles to the lumbar subarachnoid space (14). Though unquantitated, this may be associated with an increase in CSF density. If so, then theoretically a hyperbaric solution might become increasingly hyperbaric as it ascends in the subarachnoid space. The possibility that, in the head-down position, spread of a hyperbaric solution might accelerate in the upper thoracic area, because it becomes increasingly hyperbaric, seems remote.

### *Circulation of CSF*

CSF is produced, mainly by the choroid plexus, at a rate of about 0.35 ml/min (500 ml/day) in normal adults. CSF is absorbed into the venous circulation through herniations of the arachnoid that protrude into the lumina of veins through gaps in the dura (15). These herniations, the arachnoid villi, are particularly numerous in the superior sagittal sinus, but are also present in other intracranial veins. Arachnoid villi are also found adjacent to spinal nerve roots as they emerge



through the dura. The quantitative significance of spinal arachnoid villi in the absorption of CSF is unknown, but is minor compared to the role played by intracranial arachnoid villi (15). The direction of flow of the 500 ml of CSF produced per day is thus mainly intracranial from the site of production in the choroid plexus to the principal sites of vascular absorption through intracranial arachnoid villi. Downward flow of CSF through the spinal subarachnoid space is minimal, involving perhaps less than 10% of the 500 ml produced daily. Circulation of CSF in the spinal subarachnoid space in either direction is thus too slow (16) to have any significant effect on distribution of spinal anesthetic solutions in the relatively few minutes during which distribution occurs.

### *Volume of CSF*

The volume of CSF in normal adults averages about 150 ml. Approximately 75 ml is intracranial (15). The remaining 75 ml of CSF lies within the spinal subarachnoid space. The latter is the volume of CSF within which spinal anesthetics can, at least potentially, be distributed. The volume of spinal CSF within which anesthetic solutions are actually distributed under most clinical conditions is, however, substantially less than 75 ml. The exact volume of CSF below C8, the volume of most concern in spinal anesthesia, has not been quantitated. A considerable portion of this 75 ml must be in the area of the subarachnoid space occupied by the cauda equina distal, that is, caudad to L2.

The volume of CSF in the spinal subarachnoid space is decreased in the presence of chronic increases in volume of the contents of the epidural space. The epidural structures most susceptible to enlargement are the epidural veins. Chronic engorgement of epidural veins in the lumbar and lower thoracic areas, due to obstruction of normal venous effluent channels associated with an increase in intraabdominal pressure, significantly decreases the volume of CSF in the lumbar and lower thoracic subarachnoid space. This is clinically most evident in full term parturients (see below) and in patients with ascites or large intraabdominal masses. The decrease in CSF volume in the lumbar and lower thoracic areas in such patients means that the volume of CSF, in which a given volume of spinal anesthetic solution is distributed, is decreased. The result is levels of anesthesia greater than those that would be obtained if the same anesthetic solution were administered in patients in whom there is no increase in intraabdominal pressure.

The effect of term pregnancy on the distribution of spinal anesthetic solutions is graphically demonstrated by the studies of Assali and Prystowsky (17).

Using a continuous spinal technique, these authors found that 5–20 ml of 0.2% procaine was required to produce anesthesia to pinprick at the fourth cervical level (sic) in 10 normal women at term. In the same 10 women, the amount of procaine needed to obtain the same level of anesthesia 36–48 hr after delivery was 3–4 times greater. Similarly, Barclay et al. found that the injection of 4 mg tetracaine through a spinal catheter produced an average sensory level of T8 in 15 pregnant women at term (18). The same amount of tetracaine similarly injected in 20 nonpregnant women of comparable age resulted in an average level of anesthesia of T11.

### *CSF Pressure*

Conditions associated with a chronic increase in CSF pressure contraindicate lumbar puncture because of the danger of producing intracranial herniation. The effect of a chronic increase in CSF pressure on distribution of local anesthetic solutions is, therefore, of no clinical importance.

The decrease in lumbar and lower thoracic CSF volume due to epidural venous engorgement associated with increased intraabdominal pressure is not associated with an increase in CSF pressure. CSF pressure is, for example, normal in term pregnancies (19,20).

Sudden, acute increases in CSF pressure associated with labor, a Valsalva maneuver, coughing, or straining do not increase spread of spinal anesthetic solutions, clinical impressions to the contrary. In fact, neither uterine contractions nor bearing down during labor increase spinal CSF pressure (19,21,22). Such increases in CSF pressure as do occur during labor are secondary to either skeletal motor activity or transient increases in arterial pressure during labor. Even these transient increases in spinal CSF pressure have no significant effect on spread of spinal anesthetic solutions. Dubelman and Forbes, for example, found that although CSF pressure increased in (nonpregnant) patients who gave three vigorous coughs within seconds of the intrathecal injection of 12 mg hyperbaric tetracaine, the level of anesthesia was the same as it was in patients given the same amount of tetracaine who did not cough after injection (23).

Acute, transient increases in CSF pressure associated with coughing, etc., do not increase spread of local anesthetic solutions in CSF because a brief increase in CSF pressure is instantaneously transmitted throughout the entire CSF system, spinal as well as intracranial. It must be. An increase in pressure at one point in closed space filled with a noncompressible liquid is instantaneously transmitted throughout the entire system. Because no hydrostatic pressure

Table 2. Physical Characteristics<sup>a</sup> of Spinal Anesthetic Solutions at 37°C

	Density	Specific gravity	Baricity
Water	0.9934	1.0000	0.9931
CSF	1.0003	1.0069	1.0000
Tetracaine			
0.33% in water	0.9980	1.0046	0.9977
1.0% in water	1.0003	1.0007	1.0000
0.5% in 50% CSF	0.9998	1.0064	0.9995
0.5% in half normal saline	1.0000	1.0066	0.9997
0.5% in 5% dextrose	1.0136	1.0203	1.0133
Dibucaine			
0.066% in 0.5% saline	0.9970	1.0036	0.9976
Bupivacaine			
0.5% in water	0.9993	1.0059	0.9990
0.5% in 8% dextrose	1.0210	1.0278	1.0207
Procaine			
2.5% in water	0.9983	1.0052	0.9983
Lidocaine			
2% in water	1.0003	1.0066	1.0003
5% in 7.5% dextrose	1.0265	1.0333	1.0265

<sup>a</sup>Mean values.

gradients are generated in CSF during coughing, etc., no turbulence is created. The volume into which the local anesthetic solution is distributed therefore remains unaltered and the level of anesthesia is unaffected.

### Density of CSF

The density of CSF is, as discussed below, a major determinant of the distribution of local anesthetic solutions in the subarachnoid space. The mean density of normal human lumbar CSF is  $1.0003 \pm$  two standard deviations of  $0.0003$  g at  $37^\circ\text{C}$ ; the specific gravity is  $1.0069 \pm 0.0003$  (one SD) (Table 2) (24-29).

### Characteristics of Anesthetic Solutions

The physical characteristics of spinal anesthetic solutions are major determinants of their spread in CSF. The four physical characteristics that are most important are weight (i.e., density) of the anesthetic solution, the amount of anesthetic given (mg of local anesthetic injected into the subarachnoid space), the concentration of anesthetic in the injectate, and the volume of anesthetic solution injected. When one attempts to identify the individual roles of each of these four factors, one is confronted with a difficult problem. The problem arises from the fact that a change in one of these four factors is also inevitably associated with a change in at least one of the other three factors. Take, for example, studies designed to evaluate the effect on distribution of dosage of local anesthetic alone.

When the amount of local anesthetic injected is changed, then either density, volume, or concentration are also changed. Because each of the latter can also affect distribution, it becomes extraordinarily difficult to quantitate the effects of changes in dose alone. Similarly, a change in volume of injectate is associated with changes in density, dose, or concentration. The problem is further complicated by the fact that position of the patient is intimately involved in distribution of local anesthetic solutions with certain densities. The result is that there are really five, not four, factors that can determine distribution of local anesthetic solutions in CSF: four of them related to physical characteristics of the injectate, the fifth being position of the patient during and after injection. The interrelationships between these five factors make the design of controlled clinical studies of determinants of distribution of local anesthetic solutions in CSF so difficult that they are rare indeed. The value of most clinical studies is negated by failure to take into account the complex interrelationships that exist between these five factors. The following discussion is therefore restricted to those few studies designed to control, insofar as possible, each of these five factors. The role of position of the patient will be dealt with in each of the three sections devoted to the effects of density of the anesthetic solution on distribution; position and density being so closely related. The roles of dosage, concentration, and volume of injectate will then be considered in separate sections. The potential for overlap remains, nevertheless, considerable, given the fact that each factor affects another factor. For the sake of brevity and clarity, each study cited will be

summarized and discussed only once in one of the four sections.

### *Density*

The density of a solution is the weight in grams of one ml of solution (i.e., g/ml). The specific gravity of a solution is a ratio: the density of the solution divided by that of water. The baricity of a local anesthetic solution is also a ratio: the density of the solution divided by that of CSF. One way of estimating distribution of a local anesthetic solution in CSF is calculation of the ratio between the specific gravity of the local anesthetic solution and the specific gravity of CSF. This involves calculating the ratio between two ratios, each having the density of water as a common denominator. A simpler and more direct method is to rely upon baricity, the ratio between the density of the anesthetic solution and the density of CSF. If this ratio is 1.0000, the solution is isobaric. If the ratio is greater than 1.0000, the solution is hyperbaric; if less than 1.0000, it is hypobaric.

Essential to the calculation of either specific gravities or baricities of local anesthetic solutions as determinants of their distribution in CSF is assurance that densities of all solutions involved (water, CSF, and anesthetic solutions) have been measured at the same temperature. This is necessary because the density of a solution is inversely related to its temperature (24,26,27,29). Because temperatures of local anesthetic solutions rapidly equilibrate with the temperature of CSF, the clinically important densities are those measured at 37°C. The density of water at standard temperature is, by definition, 1.0000. At 37°C the density of water is 0.9934, with, again by definition, a specific gravity of 1.0000 at 37°C (Table 2). The baricity of CSF is, also by definition, 1.0000 at 37°C (see Table 2; see also references 24-29 for details on densities and specific gravities of CSF and various local anesthetic solutions cited in Table 2 and in the following text). Unfortunately, many of the data on densities, specific gravities, and baricities of local anesthetic solutions cited in the literature are not always entirely reliable. One reason for this is failure to make all measurements at 37°C. Another is use of methods that are not accurate enough to give results reproducible to the fourth decimal point, a level of precision desirable if the full potential clinical significance of the data is to be realized. A third reason is quotation of data without citation of the source from whence the figures are derived. The significance of temperature is illustrated by the fact that the density of a solution determined at room temperature may indicate it is isobaric, but at 37°C it will prove to be hy-

pobaric, not isobaric. Furthermore, the effect of temperature on density must be separately measured for each solution. The fact that the density of water decreases from 1.0000 at standard temperature to 0.9934 at 37°C does not mean that the densities of all solutions decrease similarly with the same increase in temperature. The effect of temperature on density varies from one solution to another.

The following discussion of the effects of density, specific gravity, and baricity on spread of local anesthetic solutions in CSF is predicated on the assumption that the temperature of CSF is a normal 37°C. Though clinically unquantitated, hypo- and hyperthermia would be expected to have complex, subtle effects on the distribution of local anesthetic solutions, the specific gravity and baricity of which have been determined on the basis that CSF temperature is 37°C.

### *Hypobaric Solutions*

The density of a local anesthetic solution at 37°C must be far enough below the mean density of CSF at 37°C (1.0003) to take into account the small but important normal variation in density of CSF about the figure of 1.0003 if the solution is to be hypobaric in all patients, not just in some patients. Local anesthetic solutions with baricities less than 0.9990 are predictably hypobaric in all patients.

Solutions that have been clinically demonstrated to be reliably hypobaric include those containing tetracaine or dibucaine (Table 2). A 0.33% solution of tetracaine in water has a baricity of 0.9977, provides anesthesia lasting for up to 2 hr, and is easily prepared using commercially available 1.0% solutions of tetracaine for spinal anesthesia and U.S.P. sterile distilled water without preservatives or other additives. Though not as widely used today, the commercially available 0.066% solution of dibucaine in 0.5% saline, with a baricity of 0.9967, is equally effective for hypobaric spinal anesthesia. A 0.5% dextrose-free solution of bupivacaine has a baricity of 0.9990 (Table 2). It is, therefore, slightly hypobaric in most patients, as demonstrated in the rigidly controlled studies of Chambers et al. (31), Kalso et al. (13), and Tuominen et al. (32). Dextrose-free 0.5% solutions of bupivacaine are, nevertheless, so slightly hypobaric that they are generally regarded, and are clinically used, as if they were isobaric. For this reason, 0.5% bupivacaine solution is discussed below in the section in which isobaric solutions are considered. Strongly hypobaric solutions of bupivacaine with baricities less than 0.9980, and yet with concentrations of bupivacaine adequate to provide good anesthesia and muscle relaxation, can

be prepared by adding distilled water to 0.75% bupivacaine solutions. Experience with such solutions has been too limited, however, to document their efficacy at the present time.

Hypobaric solutions of procaine, lidocaine and other local anesthetics with similar anesthetic potencies, though eminently suitable for diagnostic and therapeutic spinal anesthesia, are not satisfactory for operative hypobaric spinal anesthesia. By the time local anesthetics such as these have been diluted sufficiently to create a hypobaric solution, they are, because the anesthetics do not have the potency of tetracaine, dibucaine, or bupivacaine, approaching their minimum effective local anesthetic concentrations. A 2.5% solution of procaine in water is hypobaric (Table 2). After the intrathecal injection of 2.5% procaine in water, the solution is, however, further diluted by CSF. It is so diluted that the duration of anesthesia is so brief as to be impractical in most operations. Successful hypobaric spinal anesthesia can be achieved only with highly potent local anesthetics.

The position of the patient during, and for the first minutes after, intrathecal injection of a hypobaric solution is the major determinant of its distribution in CSF. If the patient is in the head-up position during and after injection in the lumbar area, the anesthetic solution ascends in a cephalad direction. How high it ascends depends upon how hypobaric the solution is, the degree of the head-up position, and, secondarily, upon factors discussed below (see the Volume Injected section, below). If the patient is in the head-down position during and after injection, the anesthetic solution is distributed caudad to the site of injection.

Thoracic levels of anesthesia adequate for intraabdominal operations can be achieved with hypobaric solutions injected with the patient in the head-up position. This was once a widespread technique. It is, however, a potentially dangerous technique. It is dangerous because the head-up position in the presence of extensive preganglion sympathetic denervation produced by the anesthesia may lead to severe, even calamitous, decreases in cardiac output and blood pressure (30). Hypobaric spinal anesthetics are rarely used today when levels of anesthesia to T10 or above are required. Hypobaric spinal anesthetics are, on the other hand, both effective and safe for rectal or perineal operations, especially those performed in the prone, jack-knife position. In such cases, induction of spinal anesthesia in the same position as that required for the operation assures that anesthesia will be restricted to the sacral and lower lumbar roots and that physiologic responses will be minimal—all without having to move the patient after injection. Hy-

pobaric techniques are also useful for low unilateral spinal anesthesia, especially anesthesia of only one lower extremity. Unilateral hypobaric spinal anesthesia can, however, be produced only if turbulence at the site of injection is minimized.

### *Isobaric Solutions*

Because of the slight but important variation in the density of CSF about the mean figure of 1.0003, one cannot assure that an anesthetic solution with a density of 1.0003 will prove to be isobaric in all patients. Nevertheless, there are solutions that under clinical conditions functionally behave, insofar as distribution in CSF and the resulting levels of anesthesia are concerned, as if they have the same density as CSF. Functionally isobaric solutions of tetracaine include 1% in water, 0.5% in 50% CSF, and 0.5% in half normal saline (Table 2). As mentioned above, though 0.5% bupivacaine is (barely) hypobaric (Table 2), under clinical conditions its distribution resembles that of isobaric solutions more than that of truly hypobaric solutions.

As with hypobaric solutions, the best and most reliable isobaric solutions are those that use highly potent local anesthetics. Lidocaine 2% in water is functionally isobaric (Table 2), but after dilution by CSF following injection it becomes too weak to provide anesthesia for more than short periods.

The effect of position of the patient, during and after injection of isobaric spinal anesthetic solutions, on subsequent distribution of anesthetic has been evaluated by Wildsmith et al. (33). They found that position of patients during and after injection of isobaric tetracaine solutions had no effect on the level of anesthesia. In 10 patients, 5 mg (1 ml) isobaric tetracaine was injected with patients in the seated position, and left seated for 5 min before being placed in the supine horizontal position. In another 10 patients, 10 mg (2 ml) isobaric tetracaine was injected with patients in the lateral position, and left in the lateral position for 5 min before being placed in the supine horizontal position. There was no significant difference in the levels of anesthesia in the two groups. In a comparable study, Tuominen et al. (32) determined sensory levels of anesthesia after injection of 3 ml of 0.5% bupivacaine in 10 patients in the seated position, the seated position being maintained for 2.5 min before the patients were placed in the supine horizontal position. Maximum cephalad spread averaged T7. In another 10 patients, the same volume of the same anesthetic solution was injected with patients in the lateral position and then immediately placed in the supine horizontal position. Maximum cephalad spread



averaged T8. The difference in spread was not statistically significant. The same authors also found that, when 0.75% bupivacaine was injected, the level of anesthesia was the same (T8) as it was when 0.5% bupivacaine was injected in the lateral position with immediate return to the horizontal supine position. However, when 0.75% bupivacaine was injected with patients in the sitting position, and the sitting position maintained for 2.5 min, the level of anesthesia (T4) was statistically significantly higher than when the same concentration was injected in the lateral position (T8). It was also significantly higher with 0.75% in the seated position (T8) than it was with 0.5% in the seated position (T7). The authors attributed these differences to the fact that glucose-free bupivacaine is not truly isobaric but, instead, is slightly hypobaric.

The major clinical virtue of isobaric spinal anesthetics lies in the fact that position of the patient has no effect on distribution of the anesthetic. Distribution is essentially the same if injection is made in the sitting or in the head-down position. Distribution is also unaffected by movement of the patient after injection. These attributes are clinically particularly useful when levels of anesthesia to T10 or below are required. Isobaric solutions are rarely used when levels of anesthesia in the mid-thoracic area are required; the volumes of anesthetic needed to produce a level of T5 become excessive.

### *Hyperbaric Solutions*

For an anesthetic solution to be reliably hyperbaric in all patients, it must have a baricity of at least 1.0015 at 37°C. The easiest and most widely used way to achieve this is by the addition of dextrose to the anesthetic solution. Because dextrose is neurologically benign, the concentrations of dextrose used are usually far in excess of those required to increase baricity above 1.0015. Although some authors have reported that the concentration of dextrose affects spread (34), the consensus is that once enough dextrose has been added to increase baricity of the solution above 1.0015, concentration of dextrose has little effect on distribution. Maximum cephalad spread is the same with a 5% concentration of lidocaine in 5% dextrose, for example, as it is with a 5% concentration of lidocaine in 7.5% dextrose (35), a finding also reported in a study comparing spread of bupivacaine made hyperbaric by either 5% or 8% dextrose (31,36,37). Physical characteristics of solutions made hyperbaric by the addition of dextrose are summarized in Table 2.

The distribution of hyperbaric spinal anesthetic solutions in CSF is influenced by position. If injection is made with the patient in the seated position, and

if the patient is left in the seated position for 10 min, the area of anesthesia can be restricted to sacral and lower lumbar roots. Whether only sacral roots are affected, or whether sacral and lower lumbar roots are affected, depends upon the volume of anesthetic solution injected. If hyperbaric solutions are injected with the patient in the horizontal or head-down position, distribution is significantly different than it is when injection is made with the patient seated. This is shown in the study by Wildsmith et al. (33). In one group of 10 patients, 3.0 ml (15 mg) of 0.5% tetracaine were injected with patients in the seated position; the position being maintained for 2 min before patients were placed in the supine horizontal position; the level of anesthesia averaged T8. The same dose and the same volume injected with patients in the lateral position and then immediately turned to the supine horizontal position resulted in a significantly higher level of anesthesia (T4).

Distribution of hyperbaric solutions injected with patients in the horizontal or head-down position may, however, not be as predictable and reliable as when injections are made with the patient seated. This is demonstrated by the data reported by Sinclair and associates (38). They studied 20 patients, all women, in whom 3.0 ml of 0.5% bupivacaine in 8% dextrose were injected at L3-4 with a 25-g needle while lying in the right lateral position with the table horizontal, all patients being turned immediately into the supine position after injection. In 10 patients, the table was left horizontal. In 10, the table was put in the 15° head-down position for 10 min before being returned to the horizontal position. The mean level of anesthesia was higher in the patients put in the head-down position. However, because of the wide range in levels of anesthesia in the patients placed in the head down position (C4-T4), the difference in levels between these patients and those left in the horizontal position was not statistically significant, the range of spread in the latter patients being T2-6. The authors concluded that the head-down position is not necessary to achieve levels of anesthesia adequate for intraabdominal operations, and, furthermore, its use is associated with less control over spread; the head-down position often resulting in unnecessarily high and potentially dangerous levels of anesthesia.

### *Amount of Anesthetic Injected*

Dose (i.e., mg of local anesthetic injected) was found by Pflug et al. to have no effect on distribution of local anesthetic solution in CSF. In their study, 7.5 and 15.0 mg of 0.75% hyperbaric bupivacaine (i.e., 1-2 ml) resulted in similar levels of anesthesia (39). Nolte

Table 3. Concentration and Dose of Dextrose-Free Bupivacaine and Volume of Solution Used in the 6 Groups of 12 Patients each Studied by Shesky et al. (42)

Group	Concentration (%)	Volume (ml)	Dose (mg)
I	0.5	2.0	10
II	0.5	3.0	15
III	0.5	4.0	20
IV	0.75	1.3	10
V	0.75	2.0	15
VI	0.75	2.7	20

and Stark also found no correlation between dose of 0.5% bupivacaine without dextrose and level of anesthesia (40). On the other hand, Bengtsson et al. concluded that "dosage (in mg) is more important than either volume or concentration" in determining spread of dextrose-free bupivacaine solutions (41). This conclusion was, however, based simply on the observation that injection of 4.5 ml 0.5% bupivacaine (22.5 mg) gave a level of anesthesia no different than did injection of 3.0 ml 0.75% bupivacaine (22.5 mg). Whether the experimental design in this study is adequate to support the conclusion, purely on an exclusionary basis, is debatable. In any case, these, as well as many other studies, are plagued by the problem of how to identify the role of one factor in determining spread of spinal anesthetic solutions when other important factors (dose, concentration, volume) are simultaneously being changed. The problem of multiple simultaneously operative factors has, however, been addressed in a unique and particularly elegant way by Shesky et al. (42).

What Shesky et al. did was to conduct a double-blind study in which age, height, position, and details of technique were controlled (42). Seventy-two patients were studied. All were injected with dextrose-free bupivacaine in the seated position and, after 2 min, placed in the lithotomy position with the table horizontal. The patients were divided into six groups of 12 patients each with the concentration (%) of bupivacaine, the volume (ml) injected, and the amount of bupivacaine given (mg) altered in the six groups as shown in Table 3. The number of groups studied made possible statistical comparisons that could separate out the individual roles of concentration, volume, and dose. The results showed that the levels of anesthesia were significantly higher (T2-4) in patients given 15 or 20 mg bupivacaine (groups II, III, V, and VI) than they were in patients given 10 mg (T5-8; groups I and IV). Furthermore, the levels of anesthesia were similar in patients who were given the same amount of bupivacaine (groups I and IV) even though the concentration of bupivacaine and the volume injected differed. Also, in patients who received

the same volume of anesthetic solution (2 ml), the levels of anesthesia were significantly higher in those patients given 0.75% bupivacaine (group V) than in those given the 0.5% solution (group I). The authors concluded, therefore, that "total dosage of bupivacaine is more important than volume or concentration of anesthetic solution" in determining spread of the anesthetic solution in CSF, the same conclusion arrived at by Bengtsson et al. (41). The only caveat with regard to these data is that the bupivacaine solutions used are slightly hypobaric. Thus the results may not be entirely applicable to solutions that are more clearly hypobaric, more definitely isobaric, or strongly hyperbaric. The data are, nevertheless, convincing enough to conclude that dosage has a significant effect on distribution independent of concurrent changes in concentration, volume, and baricity. But the conclusion of Shesky et al., that dosage is "more important than volume or concentration" in determining spread of anesthetic solutions is appropriate. The data of Shesky et al. do not necessarily exclude the possibility that concentration and volume are not also determinants, though secondary determinants, of the distribution of anesthetic solutions in CSF.

#### *Concentration of Anesthetic*

There is no compelling evidence that concentration of local anesthetic injected intrathecally has any significant effect per se on distribution of local anesthetics in CSF. Nor are there any theoretical reasons to expect that concentration might affect distribution, independently of changes in dosage, density, or volume of injectate, associated with changes in concentration of anesthetic in the solution injected into the subarachnoid space.

#### *Volume Injected*

The injection of a spinal anesthetic solution into the subarachnoid space causes bulk displacement of CSF away from the site of injection. The displacement of CSF by anesthetic solution at the site of injection causes

changes in neurologic function at the site of injection. The extent of changes in neurological function at the site of injection depends, however, not only upon the volume of anesthetic solution injected, i.e., the volume of CSF displaced, but also upon whether or not the injected solution disperses away from the site of injection so rapidly that neurologic function at the site of injection is altered little or not at all. Whether the anesthetic solution disperses rapidly from the site of injection depends upon the baricity of the solution injected and the position of the patient during and after injection. The effect of volume of anesthetic solution injected on subsequent distribution varies, therefore, with the baricity of the solution injected. If the solution is hypo- or hyperbaric, distribution effected by baricity will be additive to distribution effected by the volume injected. The question as to whether volume significantly affects distribution of spinal anesthetic solutions is therefore considered (below) in terms of the baricity of the anesthetic solution used.

*Hypobaric solutions.* The only controlled study of the effect of changes in the volume of injected hypobaric spinal anesthetic solutions on distribution of the solution is that of Brown et al. (2). They found that injection in the lateral position of 1.0 or 1.5 ml hypobaric tetracaine, with the patient immediately turned to the supine horizontal position, produced similar levels of anesthesia. This is perhaps not surprising because the horizontal position provided no opportunity for gravity to affect spread of the hypobaric solution. Also, the difference in volumes injected, only 0.5 ml, may have been too slight to produce clinically meaningful differences in spread.

*Isobaric solutions.* The effect of volume injected on subsequent distribution of spinal anesthetic solutions has been said to be most evident when isobaric solutions are used. The best studies on the effects of volume on distribution of isobaric solutions are those in which tetracaine has been used to formulate spinal anesthetic solutions as nearly isobaric as possible, given the normal slight variation in density of CSF mentioned above. Three studies have evaluated the effects of volume of isobaric tetracaine on distribution of tetracaine in CSF under suitably controlled clinical conditions. In one of these, that by Brown et al., 3.0 ml of isobaric 0.5% tetracaine (15 mg) produced the same levels of anesthesia (T8-9) as did 2.0 ml of the same solution, all injections being made in the lateral position with the patients then immediately turned to the supine horizontal position. Levels of anesthesia were the same in this study despite the increase in

volume (and dose) of tetracaine given (2). Similarly, when Wildsmith et al. (33) injected 1 ml of 0.5% isobaric tetracaine (5 mg) with patients ( $n = 10$ ) seated during and for 2 min after injection, the average level of anesthesia (as defined in this review) was T10. When 2.0 ml of 0.5% isobaric tetracaine were injected with the patients ( $n = 10$ ) in the lateral position during and for 5 min after injection before being turned to the supine horizontal position, the average level of anesthesia was also T10. The levels of anesthesia were the same even though both dosage of tetracaine and volume of solution injected, as well as position of the patients during and after injection were different in the two groups. Finally, McClure et al. also found that the levels of anesthesia were similar after injection of 10 mg tetracaine added to 1.0, 2.0, or 4.0 ml of normal saline when patients were turned from the lateral position to the supine horizontal position immediately after injection (9).

These data demonstrate that position of the patient during and after injection of isobaric tetracaine has no effect on distribution of tetracaine in CSF (33). The data also suggest that dose of isobaric tetracaine has no effect on distribution (2,33), a finding at variance with the finding by Shesky et al. (42) that dose of 0.5% bupivacaine is a major determinant of spread. Most important, these data also suggest that the volume of isobaric tetracaine injected has no effect on distribution: increasing the volume from 1.0 to 2 ml had no effect (2,9,33); even increasing the volume to 4.0 ml had no effect on distribution (9). Failure to see an increase in spread by increasing the volume by 1.0 ml could perhaps be attributed to the fact that a 1.0 ml increase in volume is too modest to produce clinically significant effects on distribution. Failure to see an increase in spread when the volume was increased to 4.0 ml may be related to the fact that 10 mg tetracaine crystals were added to increasing volumes of saline with a resulting decrease in specific gravity of the anesthetic solution from 1.0085 (at 25°C) with 1.0 ml, to 1.0077 with 2.0 ml, and to 1.0065 with 4.0 ml. The changes in specific gravity may have obscured the effects of changes in volume.

That the relationship between volume of isobaric tetracaine and extent of spread in CSF is clinically important is illustrated by the fact that commercially available solutions of 1.0% tetracaine, while isobaric, are not used for isobaric spinal anesthesia. They are not used because a 10 mg dose of tetracaine given in 1 ml produces profound anesthesia but, because the volume is so low, the extent of anesthesia is too limited for most operations. Increasing the volume to 2 ml increases the extent of anesthesia, but 20 mg of tetracaine is excessive for the limited amount of anes-

thetia achieved. More dilute solutions of tetracaine provide satisfactory anesthesia while permitting use of larger volume to assure adequate spread.

Parenthetically, the observation by Brown et al. (2) that 3.0 ml of 0.5% hypobaric tetracaine produced the same levels of anesthesia as did 3 ml of 0.5% isobaric tetracaine does not indicate that the spreads of hypobaric and isobaric solutions are similar, because in both instances patients were in the supine, horizontal position. In that position the distribution of a hypobaric solution would not be materially different than that of an isobaric solution.

The effects on distribution of changes in volume of dextrose-free 0.5% bupivacaine injected have been evaluated in several studies. In general, 3.0 ml of bupivacaine injected into the lumbar subarachnoid space produces anesthesia to the T7-8 level, and it is the consensus that increasing or decreasing the volume injected above or below 3.0 ml produces proportionately higher or lower levels of anesthesia (4,5,31,37,40,43,44). Under controlled clinical conditions, for example, Axelsson et al. (43) found that decreasing the volume injected to 2.0 ml significantly decreased the level of anesthesia to T10-11, but that a further decrease in volume to 1.5 ml was not associated with a further decrease in level of anesthesia. On the other hand, increasing the volume injected in this study was not associated with an increase in level of anesthesia (43). Interpretation of data on the spread of 0.5% bupivacaine is, however, difficult in terms of defining precisely the relationship between volume injected and spread of isobaric solution because dextrose-free 0.5% bupivacaine is, as mentioned above, slightly hypobaric at 37°C (13,31,32).

Isobaric solutions of mepivacaine (45,46), procaine (47), and lidocaine (48) have also been used clinically. With the exception of the lidocaine study, no attempt was made, however, to examine systematically the role of volume as a determinant of isobaric solutions of these local anesthetics. In the study of isobaric 2% lidocaine (48), whether 2 or 5 ml of solution were injected had no clinically significant effect on the level of anesthesia. The volume injected, however, was dictated by the operation to be performed. In the absence of details describing precisely how, why, and to what extent the operation altered the volumes injected, an unknown factor is introduced that makes difficult the evaluation of exactly why changing the volumes of isobaric lidocaine had no effect on distribution.

*Hyperbaric solutions.* Distribution of hyperbaric solutions away from the site of injection would be expected to be related to both the effects of gravity (po-

sition of the patient) and the volume of anesthetic solution injected. The effects of gravity and position on distribution of hyperbaric solutions have been discussed above.

That baricity of a spinal anesthetic solution is of greater importance than the volume of solution injected is demonstrated by the fact that, with patients in the supine, horizontal position, the spread of 3.0 ml hyperbaric 0.5% bupivacaine in 5% or 8% dextrose is significantly greater than is the spread of 3.0 ml of isobaric 0.5% bupivacaine (2,37). That volume is also involved in determining spread of hyperbaric solutions has been demonstrated by Axelsson et al. (49). These authors injected 1.5, 2.0, 3.0, or 4.0 ml of hyperbaric 0.5% bupivacaine in 8% dextrose in 40 patients. Injections were made with patients in the sitting position. Two minutes after injection, patients were put in the lithotomy position with the table horizontal. The results showed that maximum cephalad spread was directly related to the log volume of the solution injected. The observation by the same group of investigators that the cephalad spread of 0.5% bupivacaine without dextrose, observed under similar conditions (43), was a significant 2-2.5 segments higher than it was in this study (49), is an indication of the hypobaricity of 0.5% bupivacaine without dextrose, not evidence that hyperbaric dextrose solutions fail to affect distributions. Wildsmith et al. also found that distribution of hyperbaric tetracaine was volume-related (33). The injection of 3.0 ml of 0.5% hyperbaric tetracaine (15 mg) in patients in the lateral position, and then immediately placed in the supine horizontal, resulted in an average T4 level of anesthesia. Injection of 2.0 ml of the same solution in patients in the lateral position, and left there for 5 min before being placed in the supine horizontal position, produced average levels of anesthesia at T7. Sundnes et al. similarly found volume-related levels of anesthesia with hyperbaric 0.5% bupivacaine in dextrose (50). Injections of 1.5, 2.0, and 3.0 ml ( $n = 10$  for each) with patients in the lateral position, and then immediately turned to the horizontal supine position, gave levels of anesthesia at T10, T8, and T7, respectively. The differences in levels with 1.5 and 2.0 ml, and with 1.5 and 3.0 ml, were statistically significant; the difference between 2.0 and 3.0 ml was not.

On the other hand, Bengtsson et al., in comparing 2.0 ml of 0.75% bupivacaine with 3.0 ml of 0.5% bupivacaine, both in 8% dextrose, found no difference in maximum level of anesthesia (6). Also, Chambers et al. found that 2.0, 3.0, and 4.0 ml of 0.5% bupivacaine in 8% dextrose produced similar sensory levels of anesthesia (51). In the same study, however, 1.3, 2.0, and 3.0 ml of 0.75% bupivacaine in 8% dextrose



produced volume-related increases in levels of anesthesia; indeed, study of the 3.0 ml volume was prematurely abandoned because of the excessively high levels of anesthesia produced. Under the conditions of this study, increasing volumes of 0.75% bupivacaine were associated with increasing levels of anesthesia, while increasing volumes of 0.5% bupivacaine were not. The reason for this difference is not clear and cannot be established on the basis of the data presented.

In summary, the preponderance of data from controlled clinical studies supports clinical impression and common sense: the effects of volume of hyperbaric spinal anesthetic solutions injected are additive to the effects of gravity, position, and dosage.

### *Vasoconstrictors*

Neither epinephrine nor phenylephrine (Neosynephrine), added to spinal anesthetic solutions to prolong the duration of anesthesia, affect the distribution of iso- or hyperbaric solutions of tetracaine, lidocaine, or bupivacaine within the subarachnoid space (46,50-55). The volume of vasoconstrictor solutions added to spinal anesthetic solutions is too small to affect significantly the baricity of the anesthetic solutions.

### Conclusions

The 25 factors that conceivably could affect distribution of local anesthetic solutions can be divided into two groups. Those that have no clinically demonstrable significant effects include the following: patient weight; patient gender; the direction in which the bevel of a standard lumbar puncture needle is facing when the anesthetic solution is injected; turbulence (except under special circumstances) created either by alterations in rate of injection or by barbotage; diffusion of local anesthetic in CSF; the composition of CSF; CSF circulation; CSF pressure; concentration of local anesthetic in the solution injected; and the addition of vasoconstrictors to the local anesthetic solution. Factors that demonstrably affect distribution of local anesthetic solutions in CSF, though of widely varying clinical significance, include the following: patient age; patient height; anatomic configuration of the spinal column; the site of injection; the direction of the needle during injection; the volume of CSF; density of CSF; density and baricity of the anesthetic solution injected; the position of the patient (with hypo- or hyperbaric solutions); the dosage of local anesthetic; and the volume of anesthetic solution injected.

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## Technical Communication

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# Continuous Measurement of Intravascular pH with a Fiberoptic Sensor

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A miniaturized fiberoptic probe has been developed for continuous monitoring of intravascular pH. In this study, utilizing anesthetized dogs with the fiberoptic sensor placed in the carotid artery, comparisons were made between arterial pH as measured by the sensor and as measured using a bench instrument. The sensor was tested in both normovolemic–normotensive and hypovolemic–hypotensive states over a pH range of 6.500–7.770. The mean difference of the sensor measurements from the bench instrument measurements for 204 comparisons was  $0.060 \text{ pH} \pm 0.004$  (SEM). Overall correlation between the fiberoptic probe and the reference electrode was 0.92. The sensor performed equally well in the presence of normotension or hypotension and during respiratory or metabolic acidosis and alkalosis. Sensor drift during an experimental period of more than 6 hr was no more than  $0.042 \pm 0.006$  pH units. The fiberoptic sensor permitted continuous, reliable *in vivo* blood pH measurement without electrical connections to the subject.

Intravascular electrodes, capable of monitoring pH in a continuous manner, have been developed (1–5). Each of these pH probes has required placement of reference electrodes, with maintenance of electrical connections to the subject, and the pH reading depends, in part, on the placement site of the reference electrode. Intravascular pH sensors have not only been difficult to produce, but their consistency in performance has been difficult to achieve. Recently, a nonelectrical pH probe, based on fiberoptics and a dye sensor, has been developed (6). The use of a plastic optical fiber allows a high degree of mechanical flexibility, small size (0.2 mm diameter), ease of construc-

tion, and clinical safety. Over the physiological pH range from 7.0 to 7.4, the fiberoptic probe has been shown to agree with a standard glass pH electrode to within 0.010 pH units in buffer solutions, and to within 0.017 pH units in heparinized blood *in vitro* (7). The purpose of the present experiments was to evaluate the accuracy of the fiberoptic pH probe *in vivo* in dogs over a wide pH range. The sensor was tested in both normovolemic–normotensive and hypovolemic–hypotensive states.

## Materials and Methods

### *Experimental Animals*

Eight mongrel dogs, weighing 18–20 kg (mean  $19.2 \pm 0.6$  (SEM) kg), were used for these experiments. The animals were anesthetized with pentobarbital intravenously in loading doses of 30–40 mg/kg. Maintenance doses were given as required. The total dose of pentobarbital given over the 6-hr experimental period ranged from 50 mg/kg to 65 mg/kg. The animals were kept on a heating blanket, and esophageal temperature was monitored to maintain core temperature at  $36^{\circ}\text{C}$ – $37^{\circ}\text{C}$ . All animals were intubated and ventilated with a pressure-cycled respirator (Bird Technology, Palm Springs, CA). NIH guidelines for the use of experimental animals were followed.

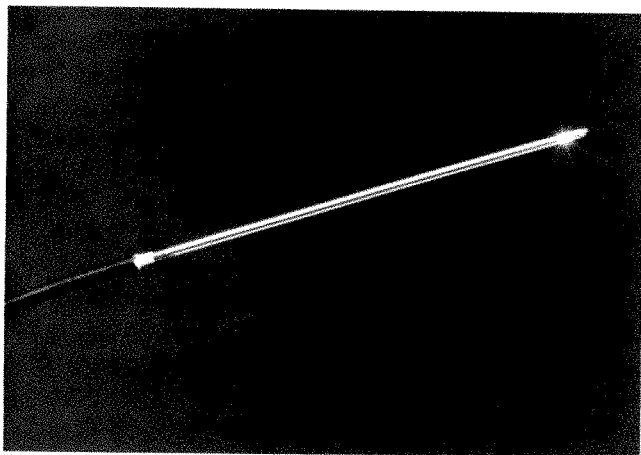
### *Intravascular Fiberoptic pH Sensor*

The fiberoptic pH probe was fashioned after the model described above (6), but was redesigned to fit into a 22-gauge stainless steel needle. Measurement of pH is based on the use of the indicator dye phenol red (phenolsulfophthalein). This dye, behaving as a weak acid, exists in two tautomeric forms, each having a different light absorption spectrum. As the pH varies, the relative size of each tautomer's optical absorption peak varies in proportion to the changing concentra-

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**Figure 1.** The fiberoptic intravascular pH sensor. The pH sensitive phenol red dye is exposed to the blood through the cellulosic dialysis membrane covered slot in the distal aspect of the 22-gauge needle. The two optical fibers extend through the needle to the phenol red dye.

tions of the acid and base forms of the dye. The changing optical absorption of the dye solution thus measures changes in pH.

Construction of the fiberoptic probe and details of the instrument have been described in detail in previous publications (6,7). Basically, the probe is constructed by bonding a single 0.125-mm diameter optical fiber (Poly-Optical Products Inc, Santa Ana, CA) into one end of a 2-mm length of cellulosic dialysis tubing (Cuprophane hollow fiber, 0.150-mm inner diameter, 0.010-mm wall thickness). A small amount of dye (phenol red that has been covalently bound to 5–10  $\mu$  diameter polyacrylamide microspheres) is then packed into the dialysis tube, and a second optical fiber bonded into the open end of the tube. The second optical fiber is then bent back onto itself, and the entire assembly slipped into a 22-gauge stainless steel needle. The assembly is then positioned within the needle so that the dialysis tubing lies in an opening provided by two slots machined in the needle wall. Once positioned, the assembly is potted into the needle with epoxy (Fig. 1).

The fiberoptic measurement system relates pH to the ratio of returned green and red light intensities. A tri-state LED (Stanley part number SPRG5111) provides alternate green and red light with a dark period between each light pulse. The ratio of the green light intensity, which varies inversely with pH, to the red light intensity, used as a reference, is determined after subtraction of the dark signal from both the green and red signals. The ratio is then converted to pH by the following relation:

$$\text{pH} = \text{pK} - \log \left[ \frac{C}{K \log R} \right]$$

where  $R$  is the red/green ratio and  $K$ ,  $C$ , and  $\text{pK}$  are probe constants. Data acquisition and processing are done with a specially designed microprocessor system (BGA-1000 CM, Orange Medical Instruments, Costa Mesa, CA) capable of monitoring up to five sensors simultaneously, and equipped with six analog outputs (five pH probes plus temperature) and an RS232C interface.

### Calibration

Each fiberoptic pH sensor ( $n = 8$ ) was calibrated with three phosphate buffers at the beginning and end of each experiment (pH 6.425, pH 6.967, pH  $7.592 \pm 0.01$  at  $37^\circ\text{C}$ ). In vitro arterial and mixed venous blood pH measurements were performed at  $37^\circ\text{C}$  (IL 1302 Blood Gas Analyzer, IL Laboratories, Boston, MA), using two buffer calibrations initially (pH 6.425, pH 7.592), and one-point calibration checks before each measurement. At the end of each experiment, the pH of each of the three initial buffers was measured with the blood-gas machine and the fiberoptic probe, and the difference in measurements calculated to determine fiberoptic probe and blood-gas equipment drift.

### Experimental Protocol

After each dog was anesthetized with pentobarbital and intubated, the femoral artery and vein were exposed bilaterally. The left carotid artery was exposed at midposition over a 2-cm length. A no. 7 French balloon-tipped, flow-directed thermodilution pulmonary artery catheter (8) was placed through one femoral vein. Bilateral femoral arterial catheters were inserted.

The remaining femoral vein was cannulated and subsequently used for the reinfusion of shed blood. The pulmonary artery and femoral artery catheters were continuously flushed with 5% dextrose solution containing 1 U/ml heparin at 3 ml/hr. Statham 23db pressure transducers (Gould Electronics, Oxnard, CA) and a Grass Model 7 4-channel recorder (Grass Instruments, Braintree, MA) were used to monitor femoral artery, pulmonary artery, right atrial, and pulmonary capillary wedge pressures. The transducers were set to the midthoracic level of the dogs and were calibrated against a mercury sphygmomanometer. The dogs were given heparin (100 U/kg) intravenously. Supplemental doses of heparin (50 U/kg) were given every 2 hr. The fiberoptic pH sensor was inserted into



Table 1. Cardiorespiratory Variables Utilized in the Study

Abbreviation	Variable	Formulae of derived variables
CaO <sub>2</sub>	Arterial oxygen content	
Cv̄O <sub>2</sub>	Mixed venous oxygen content	
C(a-̄v)O <sub>2</sub>	Arterial-mixed venous oxygen content difference	CaO <sub>2</sub> - Cv̄O <sub>2</sub>
CI	Cardiac index	CO ÷ surface area
CO	Cardiac output	
CVP	Central venous pressure	
ĐO <sub>2</sub>	Oxygen delivery	CaO <sub>2</sub> × CI × 10
HR	Heart rate	
LCWI	Left cardiac work index	CI × MAP × 0.0144
MAP	Mean arterial pressure	
MPAP	Mean pulmonary arterial pressure	
O <sub>2</sub> ext	Oxygen extraction ratio	(CaO <sub>2</sub> - Cv̄O <sub>2</sub> ) ÷ CaO <sub>2</sub>
PVRI	Pulmonary vascular resistance index	79.92 (MPAP - WP) ÷ CI
RCWI	Right cardiac work index	CI × MPAP × 0.0144
SaO <sub>2</sub>	Arterial oxygen saturation	
SVRI	Systemic vascular resistance index	79.96 (MAP - CVP) ÷ CI
Temp	Pulmonary artery blood temperature	
VO <sub>2</sub>	Oxygen consumption	C(a - v̄)O <sub>2</sub> × CI × 10
PCWP	Pulmonary capillary wedge pressure	

the exposed carotid artery and the area was covered with saline soaked gauze pads.

Ventilation was maintained with 100% oxygen. A controlled ventilatory mode was utilized. Peak inspiratory pressures were kept below 30 mm Hg.

Data sets included measurement of arterial and mixed venous (pulmonary artery) pH, PCO<sub>2</sub>, and PO<sub>2</sub>. The fiberoptic pH catheter value was recorded at the same time as the arterial blood specimen was withdrawn. At the same time, systemic arterial, right atrial, pulmonary artery, and pulmonary capillary wedge pressures were recorded. Cardiac output was measured in duplicate, using injection of 10 ml of a 5% solution of dextrose in water at 0°C through the proximal port of the pulmonary artery catheter with integration of results by a cardiac output computer (Santa Barbara Medical Instruments, Santa Barbara, CA). Derived cardiorespiratory variables were calculated by standard formulae (9). The cardiorespiratory variables utilized in the study and their abbreviations are shown in Table 1.

Data sets were collected at least every 15 min throughout the experiment. After a 45-min period of stabilization (stage 1), blood was withdrawn (stage 2) at the rate of 50 ml every 3 min until the mean arterial pressure (MAP) decreased to 40 mm Hg. Data sets were collected after each bleed. When a blood pressure of 40 mm Hg (stage 3) was achieved, the blood collection reservoir was placed at a height to maintain MAP at this level. After a 30-min stabilization period with an MAP of 40 mm Hg, the respiratory rate was

increased to 40 breaths/min (stage 4). Hyperventilation was continued for 30 min unless reinfusion of more than 250 ml of shed blood was required to keep MAP at 40 mm Hg, in which case the hyperventilation was terminated. After 30 min of hyperventilation, the animal was then given 167 mEq NaHCO<sub>3</sub> (3 ampules) to induce metabolic alkalosis in addition to the respiratory alkalosis (stage 5). The respiratory rate was then decreased to 5 breaths/min (stage 6) for 30 min. After the hypoventilation stage, the respiratory rate was increased back to the baseline level, 12-14 breaths/min (stage 7). The animal was kept at this hypotensive stage until 25% of the shed blood had been taken up to maintain the blood pressure at 40 mm Hg. When 25% of the shed blood had been reinfused, the remaining blood was returned to the animal and data collected over a 30-min period (stage 8). After this stage, the animals were sacrificed.

### Data Analysis

Data are presented as means ± SEM. Comparison of cardiorespiratory values to the control group (stage 1) was performed using analysis of variance and the Dunnett's test. Regression coefficients were calculated by the least-squares method.

### Results

Table 2 shows the measured and derived cardiorespiratory values for each stage of the experiment. Blood

Table 2. Cardiorespiratory Measurements during the Experiment

Variable	Stages of the experiment							
	1	2	3	4	5	6	7	8
HR (beats/min)	154 ± 8	146 ± 7	146 ± 15	162 ± 11	175 ± 15	156 ± 11	183 ± 7	147 ± 10
RR (breaths/min)	12 ± 1	12 ± 1	13 ± 1	39 ± 1 <sup>b</sup>	28 ± 5 <sup>a</sup>	5 ± 0 <sup>c</sup>	14 ± 2	16 ± 5
MAP (mm Hg)	141 ± 8	112 ± 7 <sup>b</sup>	41 ± 2 <sup>b</sup>	43 ± 5 <sup>b</sup>	52 ± 5 <sup>b</sup>	42 ± 3 <sup>b</sup>	45 ± 3 <sup>b</sup>	109 ± 10 <sup>b</sup>
CVP (mm Hg)	1 ± 1	0 ± 1	-1 ± 1	-1 ± 1 <sup>a</sup>	0 ± 2	-2 ± 1 <sup>a</sup>	-1 ± 1	5 ± 1 <sup>a</sup>
MPAP (mm Hg)	11 ± 1	6 ± 1 <sup>a</sup>	4 ± 1 <sup>b</sup>	4 ± 1 <sup>a</sup>	5 ± 2 <sup>a</sup>	6 ± 1 <sup>a</sup>	5 ± 1 <sup>a</sup>	24 ± 2 <sup>b</sup>
PCWP (mm Hg)	3 ± 1	0 ± 1 <sup>a</sup>	0 ± 1 <sup>a</sup>	0 ± 1 <sup>a</sup>	0 ± 2	0 ± 1 <sup>a</sup>	0 ± 1 <sup>a</sup>	10 ± 2 <sup>a</sup>
CI (L·min <sup>-1</sup> ·M <sup>-2</sup> )	3.5 ± 0.4	1.9 ± 0.2 <sup>a</sup>	1.1 ± 0.1 <sup>b</sup>	1.0 ± 0.2 <sup>a</sup>	1.7 ± 0.3 <sup>a</sup>	1.6 ± 0.2 <sup>b</sup>	1.3 ± 0.2 <sup>b</sup>	5.9 ± 0.4 <sup>b</sup>
SVRI (dsec/cm <sup>5</sup> ·M <sup>2</sup> )	3527 ± 487	5894 ± 985 <sup>a</sup>	3605 ± 411	4296 ± 953	3416 ± 988	2676 ± 600	3679 ± 852	1432 ± 157 <sup>a</sup>
PVRI (dsec/cm <sup>5</sup> ·M <sup>2</sup> )	173 ± 14	281 ± 17 <sup>b</sup>	343 ± 40 <sup>b</sup>	336 ± 83	312 ± 72	380 ± 75 <sup>a</sup>	488 ± 121 <sup>a</sup>	182 ± 18
LCWI (g/M <sup>2</sup> )	7.1 ± 0.9	3.4 ± 0.5 <sup>b</sup>	0.7 ± 0.1 <sup>b</sup>	0.6 ± 0.1 <sup>a</sup>	1.4 ± 0.5 <sup>a</sup>	1.0 ± 0.1 <sup>b</sup>	0.8 ± 0.2 <sup>b</sup>	9.3 ± 1.1
RCWI (g/M <sup>2</sup> )	0.57 ± 0.12	0.19 ± 0.03 <sup>a</sup>	0.08 ± 0.02 <sup>a</sup>	0.07 ± 0.03 <sup>a</sup>	0.21 ± 0.11 <sup>a</sup>	0.16 ± 0.04 <sup>a</sup>	0.11 ± 0.04 <sup>a</sup>	2.06 ± 0.30 <sup>b</sup>
Temp (°C)	36.8 ± 0.5	36.2 ± 0.5	36.1 ± 0.6 <sup>a</sup>	36.1 ± 0.9	36.5 ± 0.6	37.1 ± 0.6	37.1 ± 0.6	36.9 ± 0.7
Hct	38.4 ± 2.1	39.2 ± 1.7	33.3 ± 2.6	28.4 ± 2.5 <sup>a</sup>	19.8 ± 0.6 <sup>b</sup>	24.6 ± 1.3 <sup>a</sup>	23.5 ± 1.3 <sup>a</sup>	31.9 ± 1.5 <sup>a</sup>
PaO <sub>2</sub> (torr)	447 ± 24	420 ± 23	399 ± 27	393 ± 27 <sup>a</sup>	422 ± 31	396 ± 29 <sup>a</sup>	395 ± 29 <sup>a</sup>	425 ± 45
PaCO <sub>2</sub> (torr)	31 ± 3	29 ± 3	37 ± 6	29 ± 3 <sup>a</sup>	47 ± 7 <sup>a</sup>	64 ± 4 <sup>a</sup>	45 ± 4 <sup>a</sup>	65 ± 4 <sup>a</sup>
HCO <sub>3</sub>	19.0 ± 1.1	17.4 ± 1.1 <sup>a</sup>	16.2 ± 1.8	14.8 ± 3.5	41.2 ± 4 <sup>b</sup>	26.4 ± 4.4	24.0 ± 3.8	29 ± 2 <sup>b</sup>
O <sub>2</sub> sat (%)	99.8 ± 0.0	99.8 ± 0.0	99.8 ± 0.0	99.8 ± 0.0	99.8 ± 0.0	99.8 ± 0.0	99.8 ± 0.0	99.7 ± 0.1
PvO <sub>2</sub> (torr)	57 ± 5	41 ± 3 <sup>a</sup>	31 ± 3 <sup>a</sup>	24 ± 2 <sup>a</sup>	30 ± 5 <sup>a</sup>	31 ± 3 <sup>a</sup>	25 ± 2 <sup>b</sup>	73 ± 5
PvCO <sub>2</sub> (torr)	35 ± 4	37 ± 3 <sup>a</sup>	57 ± 7 <sup>a</sup>	53 ± 5 <sup>b</sup>	67 ± 8 <sup>a</sup>	77 ± 5 <sup>b</sup>	70 ± 5 <sup>b</sup>	73 ± 4 <sup>b</sup>
pH <sub>v</sub>	7.361 ± 0.029	7.323 ± 0.021 <sup>a</sup>	7.136 ± 0.040 <sup>b</sup>	7.131 ± 0.089 <sup>a</sup>	7.402 ± 0.032	7.129 ± 0.052 <sup>a</sup>	7.210 ± 0.042 <sup>a</sup>	7.201 ± 0.018
HCO <sub>3</sub>	19.5 ± 1.1	19.3 ± 1.2	19.2 ± 1.7	18.5 ± 3.2	41.3 ± 3.2 <sup>b</sup>	26.8 ± 3.8	28.8 ± 2.9 <sup>a</sup>	28.9 ± 1.9 <sup>a</sup>
O <sub>2</sub> sat (%)	85.9 ± 2.3	68.6 ± 2.0 <sup>b</sup>	37.8 ± 3.8 <sup>b</sup>	28.9 ± 5.1 <sup>b</sup>	47.8 ± 6.0 <sup>a</sup>	39.8 ± 4.5 <sup>b</sup>	31.7 ± 3.7 <sup>b</sup>	88.6 ± 2.0
CaO <sub>2</sub> (ml/dl)	18.0 ± 1.0	18.4 ± 0.8	15.6 ± 1.2	13.3 ± 1.2 <sup>a</sup>	9.3 ± 0.3 <sup>b</sup>	11.5 ± 0.6 <sup>a</sup>	11.0 ± 0.6 <sup>a</sup>	14.9 ± 0.7 <sup>a</sup>
CvO <sub>2</sub> (ml/dl)	15.6 ± 1.2	12.7 ± 0.8 <sup>a</sup>	6.0 ± 0.9 <sup>b</sup>	3.7 ± 0.5 <sup>b</sup>	4.4 ± 0.5 <sup>b</sup>	4.6 ± 0.6 <sup>b</sup>	3.6 ± 0.6 <sup>b</sup>	13.2 ± 0.6 <sup>a</sup>
C(a-v)O <sub>2</sub> (ml/dl)	2.4 ± 0.3	5.7 ± 0.3 <sup>b</sup>	9.6 ± 0.8 <sup>b</sup>	9.6 ± 1.3 <sup>a</sup>	4.9 ± 0.6 <sup>a</sup>	6.9 ± 0.6 <sup>b</sup>	7.4 ± 0.4 <sup>b</sup>	1.7 ± 0.4
Do <sub>2</sub> (ml/min·M <sup>2</sup> )	641 ± 91	349 ± 48 <sup>a</sup>	161 ± 15 <sup>b</sup>	128 ± 19 <sup>a</sup>	156 ± 28 <sup>a</sup>	187 ± 28 <sup>a</sup>	140 ± 28 <sup>b</sup>	875 ± 66 <sup>a</sup>
VO <sub>2</sub> (ml/min·M <sup>2</sup> )	75 ± 5	84 ± 7	96 ± 9 <sup>a</sup>	87 ± 9	71 ± 17	108 ± 16	92 ± 17	100 ± 23
O <sub>2</sub> Ext (%)	0.14 ± 0.02	0.31 ± 0.02 <sup>b</sup>	0.62 ± 0.04 <sup>b</sup>	0.71 ± 0.05 <sup>b</sup>	0.52 ± 0.06 <sup>a</sup>	0.60 ± 0.05 <sup>b</sup>	0.68 ± 0.04 <sup>b</sup>	0.11 ± 0.02

Data are expressed as mean ± SEM.

<sup>a</sup>*p* < 0.05 vs control (stage 1).<sup>b</sup>*p* < 0.001 vs control (stage 1).

**Table 3.** Correlation between the Fiberoptic pH Sensor and the Reference pH Electrode Values Are Expressed as mean  $\pm$  SEM

Stage	pH (reference electrode)	Range	pH (fiberoptic)	Range	Correlation ( <i>r</i> )	Number of measurements
1	7.400 $\pm$ 0.014	7.298–7.536	7.363 $\pm$ 0.016	7.281–7.541	0.90	25
2	7.360 $\pm$ 0.005	7.216–7.466	7.325 $\pm$ 0.006	7.232–7.459	0.88	78
3	7.220 $\pm$ 0.033	6.750–7.501	7.159 $\pm$ 0.033	6.720–7.500	0.92	26
4	7.285 $\pm$ 0.066	7.112–7.770	7.216 $\pm$ 0.064	7.028–7.770	0.97	12
5	7.565 $\pm$ 0.029	7.427–7.720	7.516 $\pm$ 0.029	7.428–7.716	0.93	15
6	7.215 $\pm$ 0.032	6.979–7.377	7.151 $\pm$ 0.036	6.947–7.298	0.90	16
7	7.318 $\pm$ 0.052	6.500–7.474	7.274 $\pm$ 0.053	6.478–7.435	0.99	19
8	7.243 $\pm$ 0.012	7.191–7.298	7.208 $\pm$ 0.014	7.143–7.272	0.89	13
All stages combined	7.341 $\pm$ 0.010	6.500–7.770	7.281 $\pm$ 0.010	6.478–7.770	0.92	204

**Table 4.** Fiberoptic pH Sensor Performance over Different pH Ranges

pH	Difference between reference electrode and fiberoptic sensor	<i>n</i>
6.500–6.999	0.071 $\pm$ 0.053	7
7.000–7.199	0.042 $\pm$ 0.016	32
7.000–7.400	0.055 $\pm$ 0.004	181
7.601–7.770	0.065 $\pm$ 0.018	7
Overall	0.060 $\pm$ 0.004	204

pressure was maintained close to 40 mm Hg except during stage 5 (metabolic alkalosis). Increased blood pressure during stage 5 was caused by the rapid increase in intravascular volume due to the injection of NaHCO<sub>3</sub>. PaO<sub>2</sub> was consistently greater than 300 mm Hg as a result of 100% oxygen administration.

The relationship between the fiberoptic pH sensor and bench reference determinations of pH is presented in Table 3. The correlation between the two sensors was greater than 0.88 during all stages of the experiment. The highest correlation coefficients ( $r = 0.97$ ) were found during the hyperventilation and late shock stages of the experiment. Correlation was similar when the cardiac index was less than 2.0 L·min<sup>-1</sup>·M<sup>-2</sup> ( $r = 0.89$ ) and when cardiac index was greater than 2.0 L·min<sup>-1</sup>·M<sup>-2</sup> ( $r = 0.92$ ).

The fiberoptic sensor consistently provided values lower than those measured by the blood-gas machine. The average difference between the fiberoptic sensor and the reference electrode was slightly greater during the hypotensive phases of the experiment, as compared to the control period and the period after reinfusion of all shed blood. However, the mean difference between the fiberoptic sensor and the reference electrode at any stage of the experiment was never greater than 0.069 units.

The performance of the fiberoptic pH sensor at different reference pH ranges is presented in Table 4.

Even at the extremes of pH (i.e., <7.0 and >7.6) the mean difference between the fiberoptic sensor and the reference electrode was less than 0.071 units.

Table 5 shows data on the stability of the fiberoptic pH sensor. Mean drift over the 6 hr of the experiment was never greater than 0.042 pH units. The greatest drift for an individual sensor was 0.155 pH units as compared to the pH 6.425 buffer solution. However, this sensor only differed by 0.057 units and 0.054 units from the more physiologic pH buffers of pH 6.968 and pH 7.592. For the two buffers bracketing the physiologic pH range, pH 6.968 and pH 7.592, no individual sensor showed drift greater than 0.057 units over the more than 6-hr course of the experiment.

There were no significant problems in the functioning of the fiberoptic sensors during these experiments. One sensor could not be calibrated to the buffer solutions during the initial calibration phase of an experiment and was found to have a tear in the dialysis membrane. No dysfunction of the sensors, once inserted, was observed. Alterations in fiberoptic pH values occurred if the sensor slipped from the lumen of the carotid artery, but were rapidly corrected by reinsertion of the sensor.

## Discussion

The fiberoptic pH sensor utilized in these experiments has significant advantages over previously developed methods for continuous intravascular measurement of pH. An important safety feature for human and experimental use is that no electrical connection to the body is involved. The use of a plastic optical fiber allows a high degree of mechanical flexibility. Although the sensor used in these experiments was placed in a 22-gauge needle, further miniaturization is possible, as demonstrated by the construction of similar fiberoptic pH sensors that fit into 25-gauge needles. The basic configuration of the sensor is such

Table 5. Stability of the Fiberoptic Sensor as Determined at the End of Each Experiment ( $n = 8$  sensors)

pH Buffer	Drift (pH reference electrode-pH fiberoptic)
6.425	$0.041 \pm 0.026$
6.967	$0.042 \pm 0.006$
7.592	$0.039 \pm 0.005$

that the probes are relatively inexpensive and can be considered disposable.

The experiments described in this study demonstrate that the fiberoptic probe tracks intraarterial pH in a consistent manner even at the extremes of physiologic conditions. Sensor performance was similar under normotensive and hypotensive conditions, and in states characterized by normal or low cardiac output. The difference between fiberoptic and reference electrode pH determinations averaged  $0.060 \pm 0.004$  pH units. The maximum difference between the fiberoptic sensor and reference electrode was never greater than 0.12 pH units.

The intravascular fiberoptic sensor measures blood pH at the animal's core body temperature, which, during the hemorrhagic hypotension phases of these experiments, was as much as  $0.9^{\circ}\text{C}$  less than the  $37^{\circ}\text{C}$  blood temperature used by the reference electrode. Temperature correction of intravascular pH would have diminished the calculated differences between the two pH sensors. Utilization of the in vitro relationship between blood pH and temperature described by Rosenthal (10), 0.0147 pH unit reduction per  $^{\circ}\text{C}$ , would significantly diminish the observed difference in values as recorded by the fiberoptic sensor and reference pH electrode. The temperature coefficient of the fiberoptic sensor, expressed as change of pH probe indication per  $^{\circ}\text{C}$ , has been demonstrated to be 0.0065 over the temperature range of 20 to  $40^{\circ}\text{C}$  (6,7). Correction for this temperature-dependent factor also would have decreased the observed differences between the fiberoptic sensor and the reference pH electrode.

Previous studies using intravascular pH sensors of different construction than the fiberoptic probe showed measurement accuracy comparable to that demonstrated in these experiments. Coon et al. (2), using a PdO (palladium oxide) hydrogen ion-sensing electrode and Ag/AgCl reference electrode enclosed in a gas-permeable silicone polycarbonate copolymer membrane, found the difference between the intravascular sensor and the bench instrument to average  $0.044 \pm 0.003$  (SEM) pH units. Nilsson and Edwall (5), who utilized a monocrystalline antimony pH sensor for intravascular pH monitoring, achieved a mean dif-

ference of 0.059 pH units between the antimony sensor and the standard hydrogen pH electrode.

The fiberoptic pH sensor showed acceptable stability over the course of these experiments, with mean drift over more than 6 hr being less than 0.042 pH units. In vitro, the drift in calibration of the probe is less than 0.01 pH units in 2 hr (7). After storage for 2 weeks in pH 6.84 buffer solution, the calibration of the probe drifted less than 0.02 pH units (6,7). In vivo drift of the fiberoptic sensor was similar to that reported with polymer membrane coated sensors, 0.01 pH units/hour (4) or 0.05 pH units over the course of an 8-hr experiment (3).

The step response time of the fiberoptic pH sensor is 90% in 30 sec (6,7). Although this response time is slower than that described with the polymer coated electrode (2), 0.1 sec, it is certainly rapid enough for the sensor to have widespread clinical and experimental utility.

Anticoagulation with heparin was utilized in these experiments to prevent clotting on the membrane surface. Deposition of fibrin to the sensor would prevent accurate tracking of blood pH by mechanically blocking ion exchange between blood and the sensor. Clinical utility of the fiberoptic sensor will require development of an antithrombogenic coating for the probe. Several compounds suitable for use with the fiberoptic sensor are available, and we are currently evaluating their efficacy.

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## Clinical Reports

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### Sublingual Emphysema Complicating Dental Anesthesia

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The introduction of gas into soft tissues during dental procedures has been recognized since 1900 (1). Cases of subcutaneous facial emphysema characterized by rapidly progressing unilateral facial swelling have been reported. To our knowledge localized sublingual emphysema without facial involvement after a dental procedure has not been reported. We present two cases of sublingual emphysema, and discuss the etiology and potential hazards of this syndrome.

#### Case 1

A 26-month-old boy with developmental delay presented for extensive dental restoration under general anesthesia. After pretreatment with atropine 0.1 mg intravenously, anesthesia was induced with thiopental 5 mg/kg intravenously, and muscle relaxation facilitated with succinylcholine 2 mg/kg intravenously. The trachea was intubated atraumatically with a 4.5-mm uncuffed nasotracheal tube. Anesthesia was maintained with nitrous oxide and isoflurane. Prior to the initiation of the dental procedure, rubber dam isolation of the operative field was established, isolating the teeth requiring dental intervention from the rest of the oropharynx. The procedure included removal of necrotic pulpal tissue from the mandibular first and second primary molars. An air-water syringe that emits water and air under pressure was used to irrigate and dry the operative field. Upon removal of the rubber dam at the completion of the procedure, sublingual swelling that displaced the tongue upward and anteriorly was noted. The sublingual swelling was crepitant, but there was no crepitus over the face.

The tissues did not appear hemorrhagic and were not fluctuant to palpation. The child's airway was not compromised and the trachea was extubated. By the following morning the sublingual swelling had disappeared. The child made an uneventful recovery.

#### Case 2

A 4-yr-old male with anoxic encephalopathy due to a near-drowning episode presented for dental surgery under general anesthesia. Anesthesia was induced with thiopental 5 mg/kg after pretreatment with atropine 0.1 mg, succinylcholine 2 mg/kg was used to facilitate trachea intubation with an uncuffed 4.5-mm nasotracheal tube. Anesthesia was maintained with nitrous oxide and isoflurane. The dental procedure consisted of removing necrotic pulpal tissue from three mandibular primary molars and restoring them with stainless steel crowns. Rubber dam isolation and an air-water syringe were again utilized during the procedure. When the rubber dam was removed at completion of surgery, marked sublingual swelling causing upward displacement of the tongue and near obliteration of the oral cavity was noted. The sublingual swelling was tense to palpation like an air-filled balloon and the area was not discolored or fluctuant. There was no crepitus palpable over the child's face or neck. The swelling was then aspirated to rule out the possibility of hemorrhage or water collection, and no liquid was obtained. Due to pooling of secretions in the oral cavity secondary to the patient's inability to swallow effectively, the child remained intubated and was given 100% oxygen by T-piece in the recovery room. After several hours, the amount of sublingual emphysema had decreased enough to allow the child to swallow and the trachea was extubated uneventfully.

#### Discussion

The sublingual space is bounded superiorly by the mucous membrane of the floor of the mouth, inferi-

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only by the mylohyoid muscle, and laterally by the inner surface of the body of the mandible (2). Entry of air or gas into the soft tissues after dental procedures has been found to be related to use of hydrogen peroxide with subsequent release of oxygen (3), air-driven turbine handpieces (4), air-water syringes (5), increased intraoral pressure after dental extractions (6), and intraoral injury (7). Gas enters the sublingual space by passing under the mandibular periosteum after its integrity is interrupted by dental extractions or restorative procedures. Introduction of air, blood, or infection into the sublingual space results in swelling of this compartment with tongue enlargement and upward displacement. This may result in dysphonia, dysphagia, dyspnea, and drooling.

Pneumomediastinum (8), fatal air embolus (9), and subcutaneous facial emphysema have been reported with the use of air-driven rotary handpieces and air-water syringes, but always in adults and never during general anesthesia. Rosenberg et al. (10) reported a case of iatrogenic subcutaneous emphysema during general anesthesia for dental restoration in a pediatric patient in whom a left-sided facial emphysema and a slight anterior displacement of the tongue occurred prior to extubation. Milne et al. (11) reported a similar case in a mentally retarded 20-yr-old adult who required prolonged intubation after general anesthesia. The two pediatric cases reported here demonstrate that sublingual emphysema may occur as an isolated finding during dental anesthesia, and that the potential space in the sublingual area may become markedly distended. This may lead to airway compromise by obstruction or by the patient's inability to swallow and protect the airway from secretions, thus requiring prolonged intubation of the trachea, as in case 2.

To decrease the likelihood of air entry, forced air-water instrumentation is not recommended in the removal of necrotic pulpal tissue. Early detection of sublingual emphysema may be accomplished by intermittently removing the rubber dam and directly viewing the tongue and sublingual tissues, or by us-

ing transparent rather than opaque material for the rubber dam. Recommendations for management of subcutaneous facial or sublingual emphysema, should either appear intraoperatively, are that nitrous oxide be discontinued to prevent further enlargement of the air mass, and that the procedure be terminated as soon as possible to prevent further air entry. Post-operative management includes continued airway protection as indicated, positioning the head up 30° or more so as not to compound the problem with venous engorgement, and close observation during and after extubation of the trachea. Prophylactic antibiotics are also recommended, as infectious organisms can be introduced with the air (12).

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## Atomizer Modification for Nasal Administration of Cocaine and Other Drugs

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Nebulizing topically applied cocaine during procedures such as nasotracheal intubation can offer many advantages over other methods. Maximal dispersal throughout the nasal passages can be achieved and exact quantification of the delivered dosage can be monitored. The latter is particularly important when using cocaine because strict adherence to dosage limits must be assured and recorded due to the potential for toxic reactions and adverse interactions (1,2). The atomizer modification presented here not only meets these objectives but also provides a means of fulfilling state and Federal accountability for the clinical use of the controlled substance cocaine.

Cocaine is unique among local anesthetics in its ability to produce vasoconstriction, and its various clinical applications have led to different methods of administration. In certain procedures, such as excision of a nasal polyp, the effects of the drug are required in only a small, localized area. For other procedures such as nasotracheal intubation or nasal insertion of a fiberoptic instrument, the objective is maximum dispersal of the drug throughout the nasal passages. Available methods of administration differ in their ability to meet these objectives, in their ability to offer precise dosage control, and in their compatibility with narcotic control regulations.

Painting cocaine solutions or crystals of the base form onto mucosal surfaces is commonly done using cotton-tipped applicators. Packing is similar and involves the use of nasal packs, such as Webril cotton strips, soaked in a cocaine solution and placed into the nasal passages. Both techniques are useful for

localized procedures, and the effects are limited to areas that can be reached with the applicators or packs or that are affected by whatever drips off onto surrounding areas. Exact dosage is unclear because a significant amount of the solution remains on the applicator or packing. This makes dosage allowances for such techniques difficult to quantify.

Applicators have also been used specifically for local anesthesia in attempting to block the sphenopalatine ganglion. One is directed cephalad to the area of the anterior ethmoid nerve and another is directed caudal to the area of the sphenopalatine ganglion. Even though this can result in excellent local anesthesia, maximal dispersal for other purposes such as vasoconstriction is not assured even if combined with additional painting. Also, the problem of controlling dosage still exists with this technique.

Dripping the solution into the nose with a dropper is another common technique, and dispersal is increased by having the patient sniff vigorously once or twice. Dosage is more readily quantitated, but there may be an increased potential for systemic absorption because relatively large volumes travel quickly to other peripheral mucosal surfaces, such as the oropharynx and the gastrointestinal tract. This can occur even after positioning the patient supine with the head tilted back prior to administering the drops. Dispersal may also be minimal if the timing of the patient's sniffing is not coordinated with the dripping of the solution.

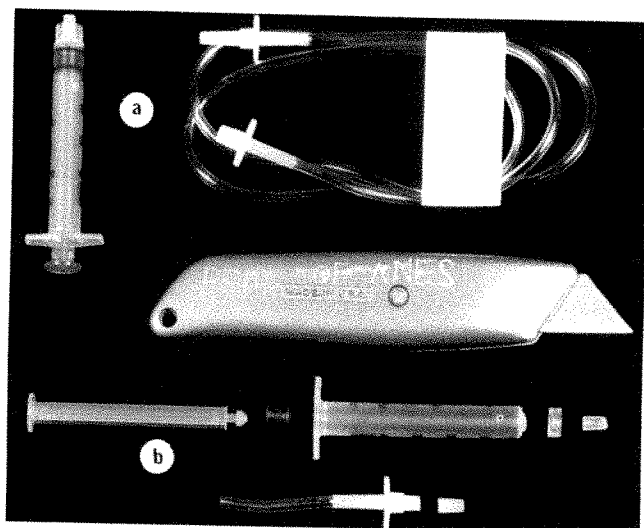
Spraying the solution is probably the optimal method of administration when maximum dispersal throughout the nasal passages is desired. Smaller total doses can be used to achieve the desired effects due to better dispersal in the nasal passages and limited transfer to other areas. Before administering the drug it is important to instruct the patient to take a breath and hold it while the actual spraying is taking place. For cases such as nasotracheal intubation where the effects of the drug are only intended for the upper air-

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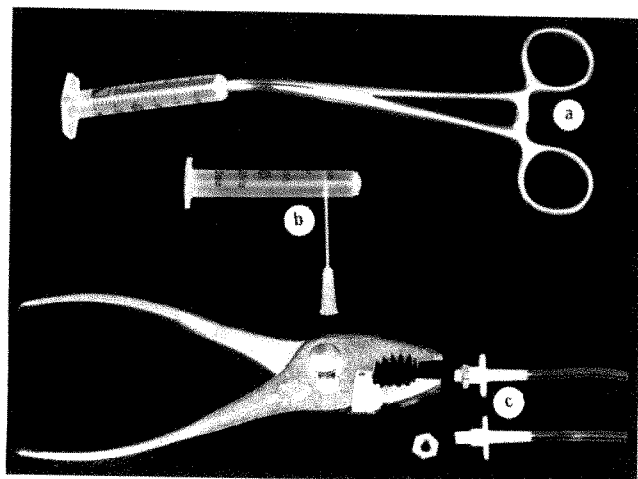
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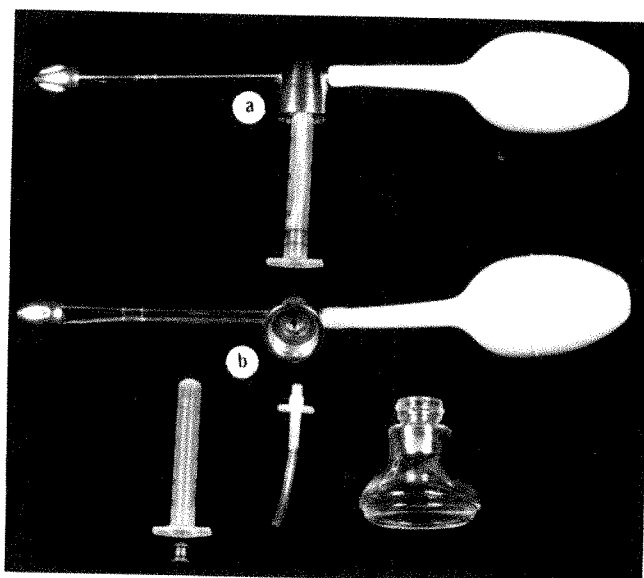
**Figure 1.** The construction materials, a 3-ml syringe and a standard intravenous extension tubing are shown (a). The Luer-lock tip is cut off the barrel of the syringe and the rubber tip of the plunger removed (b). Approximately 7 mm of the male end of the extension tubing is removed and 0.5 mm of the very tip cut off (b).



**Figure 2.** The opening on the top of the barrel is gradually dilated with the tip of a Kelly clamp until the bottom, smaller end of the extension tubing tip can be snugly inserted (a). An 18-g needle is used to make a venting port in the top of the barrel (b). This will also be used to inject the agent to be atomized into the new chamber. A 10/32 nut is used to thread the top of the extension tubing (c). This last step is optional as this portion will screw into the bottom of the Devilbiss model 15 without its own threading.

way, this will minimize the possibility of its peripheral transfer.

A specially modified atomizer has been used by several members of our anesthesia department for the past year, following its design and introduction in a clinical study of nasotracheal intubation and topical vasoconstrictors (3). We find that the results obtained with it are just as good, if not better, than with other techniques. It has also been used extensively in our



**Figure 3.** With the large glass atomizing chamber removed, the extension tubing is screwed into the threaded hole on the underside of the Devilbiss model 15 (b). The new chamber, formed from the syringe barrel, is inserted over this and slowly pushed upward until it fits snugly. The rubber plunger tip is inserted into the bottom of the barrel and slowly pushed upward until it just touches the bottom of the extension tubing. The completed atomizer is shown in the upper portion of the diagram (a). Note that the calibrations on the barrel are not accurate due to the tubing inside. Volumes of agents utilized are measured in another syringe used to inject the drug into the vent port of the new chamber.

Pulmonary Medicine Department with similar results prior to nasal insertion of fiberoptic instruments in awake patients. Additionally, the modified chamber described below offers exact quantification, control, and recording of delivered dosage. This is an important benefit unique to this device.

Although there are several atomizers available for clinical use, most have atomizing chambers that are too large for use with a controlled and potentially toxic agent like cocaine. A smaller chamber would allow for exact dosage control and thus be safer for the patient, allow for better clinical documentation in the event of adverse reactions, and be more consistent with narcotic control regulations. A modified atomizing chamber for the Devilbiss model 15 atomizer, common to many anesthesia departments, was recently developed during the study of topical nasal vasoconstrictors previously mentioned.

The modified chamber has no effect on the droplet size normally produced by the Devilbiss atomizer. The droplet size depends on several factors, including the solution used and differences in pressure exerted on the bulb. What usually results is a coarse spray that is well suited for administering topical nasal agents. In a recent communication, engineers from the man-



ufacturer stated that the range of droplet size has never been calculated for this instrument. Under most clinical conditions the droplets should not approach the 0.5- to 3.0- $\mu$ m diameter associated with peripheral transfer to the lower airways (4). However, it would still be wise to observe the precautions noted previously when peripheral transfer of the drug is not desired.

The modified chamber is constructed easily from a 3-ml syringe and the distal end of an intravenous extension (Figs. 1-3). It is inexpensive, reusable, and well-suited for clinical uses of cocaine where atomization is desirable. The solution of known concentration of cocaine, or alternative agent, is drawn up into a syringe and a specific volume injected into the vent port of the atomizer chamber. Volumes as small as

0.1 ml can be completely and accurately atomized by this instrument. The nasal tip of the atomizer can be cleaned easily after each use, making its employment with agents such as oxymetazoline (Afrin) practical, economical, and safe for multiple patient applications.

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## Ventilatory Management of Massive Bronchial Hemorrhage by Endobronchial High-Frequency Jet Ventilation and Continuous Suctioning

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One of the most serious complications of balloon-tipped pulmonary catheterization is bronchial hemorrhage due to perforation of the pulmonary artery (1). In such cases, treatment should be directed toward controlling the bleeding and maintaining effective gas exchange. We describe an adult patient who, in the course of an operation for tetralogy of Fallot, had massive bronchial hemorrhage as a result of pulmonary artery perforation by a Fogarty balloon-tipped catheter introduced during cardiopulmonary bypass. The patient was successfully managed using intubation with an endobronchial double-lumen tube, the concomitant application of high-frequency jet ventilation (HFJV) with continuous suctioning to the affected lung, and the administration of protamine to reverse the effects of heparin.

### Case Report

The patient was a 33-yr-old male weighing 54 kg. At the age of 17 yr, cardiac catheterization disclosed the presence of tetralogy of Fallot. At the age of 31 yr, he had a modified Waterstone's anastomosis performed (aorta-right lower branch of pulmonary artery anastomosis) because of increasingly limited exercise tolerance. In December 1983, the patient underwent complete repair of the tetralogy of Fallot. Cardiac catheterization revealed right ventricular pressure of 118/0 mm Hg, left ventricular pressure 117/7 mm Hg, and main pulmonary artery pressure of 18/5 mm Hg. On physical examination, systemic blood pressure was 110/75 mm Hg, heart rate was regular at 88 beats/min, and there was slight cyanosis of the lips and clubbing of the fingers. The hematocrit was 69%, there were

$7.99 \times 10^4$  red blood cells/mm<sup>3</sup>, and hemoglobin was 22.2 g/dl. Arterial blood gas analysis showed a PaO<sub>2</sub> of 75 mm Hg, a PaCO<sub>2</sub> of 38 mm Hg, pH 7.38, and SaO<sub>2</sub> 87% while breathing room air. An electrocardiogram revealed right ventricular hypertrophy and pulmonary P waves. The chest x-ray disclosed a large cardio-thoracic ratio (65%).

The patient was premedicated with diazepam (10 mg) orally 1 hr before induction of anesthesia, and with scopolamine (0.4 mg) and morphine (10 mg) intramuscularly 30 min before induction. After preoxygenation, the patient was anesthetized with morphine (1 mg/kg) and diazepam, followed by pancuronium for tracheal intubation. Sixty minutes after the induction of anesthesia, cardiopulmonary bypass was instituted. Insufflation with oxygen at 10 cm H<sub>2</sub>O was applied to the lungs during cardiopulmonary bypass. Surgery included ventricular septal defect closure using a Dacron patch, and replacement of the pulmonary valve after incision of right ventricle and main pulmonary artery. Just before the closure of right ventricular wall, a Fogarty biliary balloon probe (6F, 23 cm, American Edwards Lab.) was introduced into the lower branch of right pulmonary artery. The balloon was inflated with 1 ml of saline, and then the catheter was withdrawn in an attempt to dilate the vessels. After closing the right ventricle, partial perfusion via cardiopulmonary bypass was combined with manual ventilation with 100% oxygen. At that time, the anesthesiologist suddenly noted impaired ventilation and bleeding from the tracheal tube. Suctioning yielded 500 ml of blood within 5 min. The pleural surfaces were examined, but did not appear hemorrhagic, and therefore total cardiopulmonary bypass perfusion was reinstituted, whereupon bleeding appeared to decrease somewhat.

Flexible fiberoptic bronchoscopy disclosed bleeding from the right bronchus into the left lung. A left-sided endobronchial double-lumen tube (Portex, 6.0-mm inner diameter, each) was inserted, and clearing

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of the left and right airways was attempted by repeated suctioning.

The left lung was ventilated with oxygen in the control mode, and the right lung was manually ventilated. Cardiopulmonary support was then discontinued. After 20 min, the patient's blood pressure was, with the aid of dopamine infusion ( $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and blood transfusion, 65/40 mm Hg, heart rate 120 beats/min. Repeated suctioning of the right bronchus was necessary, however, to remove an additional 800 ml of blood. Blood gas analysis revealed  $\text{PaO}_2$  89 mm Hg,  $\text{PaCO}_2$  67 mm Hg, and pH 7.19. High-frequency jet ventilation with oxygen (respiratory rate, 200 breaths/min; driving pressure, 30 psi; I/E, 0.2) combined with continuous suctioning were applied to the affected lung. For HFJV, a VS-600 high-frequency jet ventilator (Instrument Development Corp.) was connected to a 14-gauge cannula passed through a drilled opening in a Briggs adaptor, with the tip of the cannula extending to a depth approximately 1 cm inside the tube. A suction tube was inserted through the open end of the adaptor. Ten minutes after the applications of HFJV and continuous suctioning of blood, blood gas analysis revealed  $\text{PaO}_2$  218 mm Hg,  $\text{PaCO}_2$  50 mm Hg, and pH 7.32. Blood pressure increased to 110/70 mm Hg, and the heart rate was 90 beats/min. Heparinization was reversed by administration of protamine. During the ensuing 30 min, continuous suctioning removed an additional 600 ml of blood (total bronchial blood loss 1900 ml), after which the bronchial bleeding ceased.

A postoperative chest x-ray showed an infiltrate throughout both lungs; most prominent in the area of the right lower lobe. This was interpreted as a result of intrapulmonary hemorrhage. Twenty hours after the operation, vital signs became stabilized, and only small amounts of blood were suctioned through the bronchial lumen. The endobronchial tube was replaced with a single lumen tube (Portex, 9.0-mm inner diameter) and muscle relaxants were discontinued. Three days after the operation, the trachea was extubated with acceptable blood gases and improved roentgenographic findings. The patient was discharged one month after the operation without further complications.

## Discussion

Though the balloon-tipped pulmonary catheter is routinely employed for the hemodynamic monitoring of critically ill patients, there are few reports of endobronchial hemorrhage after rupture of pulmonary artery by the catheter (2-5). In our patient, a Fogarty

biliary balloon probe was introduced into the right lower branch of pulmonary artery in an attempt to dilate the vessel prior to discontinuation of cardiopulmonary bypass. The catheter damaged the pulmonary artery in a manner similar to that seen with the Swan-Ganz catheter (3).

In our patient, the reinstitution of total perfusion during cardiopulmonary bypass was thought to be of major importance, as suggested by Rice et al. (6). When cardiopulmonary bypass was reinstituted, arterial oxygenation was well maintained and the endobronchial bleeding was decreased by reducing pulmonary blood flow, and the site of bleeding could then be determined by fiberoptic bronchoscopy. Subsequent intubation with an endobronchial double-lumen tube provided both a route for removal of blood from the bronchus and protection and ventilation of the uninvolved lung (4).

Proper ventilation settings are of primary importance in facilitating the weaning from cardiopulmonary bypass. In our patient, the damage was probably far more severe than is usually the case with pulmonary artery rupture by a Swan-Ganz catheter. Further, heparinization increased the amount of the bleeding from the bronchial tree. This bleeding and the suspension of manual ventilation during the repeated suctioning impaired gas exchange in the affected lung. In addition, the efficiency of the left lung ventilation seemed to be reduced due to the previous blood overflow from the right lung, as reflected in low  $\text{PaO}_2$  and high  $\text{PaCO}_2$ . Continuous suctioning successfully cleared the blood from the bronchial tree, thereby allowing effective gas exchange by endobronchial HFJV. Bronchial HFJV is the only means of ventilation that allows suctioning of blood while still ventilating the affected lung because HFJV includes an open system into which a suction catheter can be introduced. Reversal of the effects of heparin by administration of protamine finally stopped the bleeding into the bronchus (6).

In conclusion, the simultaneous use of endobronchial HFJV and continuous suctioning offers an excellent means for ventilatory management of the patient suffering from massive endobronchial hemorrhage. The technique could also be used during bronchoalveolar lavage or unilateral lung lavage.

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## A Method for Detection of Incompetent Unidirectional Dome Valves: A Prevalent Malfunction

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Incompetency, a common problem with unidirectional dome valves (UDVs) on anesthesia machines, is usually caused by a damaged or sticky valve, by a replaced valve of improper size, or by an irregularity on the annular seat (1). We experienced incidences of serious intraoperative hypercarbia in pediatric patients caused by incompetent inhalation UDVs on two different anesthesia machines. These two anesthesia machines had been in active clinical service, mainly for adult patients, without apparent problems. After these cases, a spot check of the UDVs in our hospital revealed some degree of incompetency in 6 of 30 machines. These findings prompted us to develop a simple and sensitive method for testing UDV competency. Using this method, a mail survey was conducted to determine the prevalence of UDV incompetency in other hospitals.

### Materials and Methods

Survey sheets were mailed to prospective correspondents, requesting them to test the competency of UDVs on their anesthesia machines using our method. The prospective correspondents were anesthesiologists and anesthesiologists who were known to one of the authors, or were anesthesia equipment managers in institutions with approved anesthesia residency programs. The following is the method modified from the original protocol used in the survey so as to include the addition of a method for detecting irregularity on the annular seat.

- A) Preparation. Remove breathing tubes from the circle, turn off all gas flows, and close pop-off valve.

- B) Checking inhalation valve (Fig. 1A). Connect a reservoir bag at the usual bag connector site and one limb of the corrugated tube on the inhalation outlet; while the exhalation inlet is covered with the palm of the hand, apply positive pressure (approximately 5–10 cm H<sub>2</sub>O) to the corrugated tube with "gentle slow blow."
- C) Checking exhalation valve (Fig. 1B). Connect a reservoir bag to the exhalation inlet and a corrugated tube on the bag connector site; while the inhalation outlet is covered with the palm of the hand, apply gentle positive pressure to the corrugated tube as described above.
- D) Interpretation of test. If the valve being tested is competent, the reservoir bag will not fill; filling of the reservoir bag indicates incompetency of the valve tested; if the incompetency is not corrected after replacement of the suspected valve, look for an irregularity on the annular seat.

### Results

From 363 survey sheets mailed, 55 institutions responded. In these institutions, a total of 715 anesthesia machines were tested for UDV competency. Ninety-three percent of 715 machines were manufactured by three major companies (Ohio, 51%; Foregger, 22%; Dräger, 20%). No incompetent UDVs were found in 21 hospitals. Either one or both UDVs were found to be incompetent in 108 machines (15%) among the 34 remaining hospitals. The highest frequency of incompetency was found in the Foregger machines (25%), the next highest (15%) in the Ohio machines, and the least (5%) in the North American Dräger (Table 1).

### Discussion

An incompetent UDV causes rebreathing of expired air during anesthesia. However, the resultant hyper-

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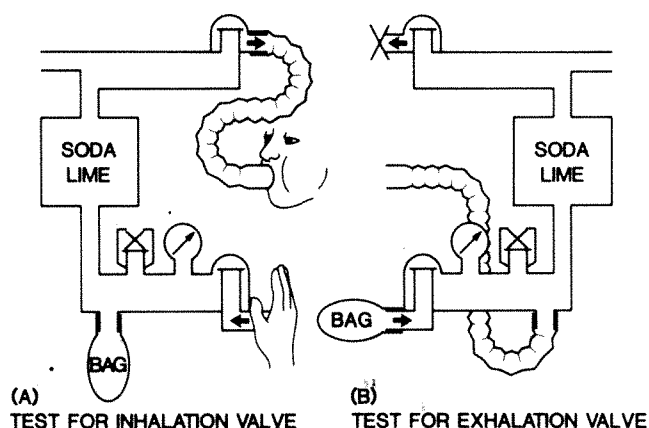


Figure 1. Schematic diagram illustrates how to connect the reservoir bag and corrugated tube for the competency test of inhalation (A) and exhalation (B) unidirectional dome valves. Arrows indicate direction of valve. See text for details.

carbia without hypoxia is not easily diagnosed because clinical signs are usually either absent in mild cases or nonspecific even in severe cases. Peak airway pressure, chest excursion, and breath sounds are not affected by the incompetent UDV because the tidal volume delivered to the patient is not altered. Unsuspected incompetency of UDVs is most frequently detected by measurements of arterial blood gas tensions or  $\text{PCO}_2$  in end-tidal or inspired air (2,3). Despite clinically adequate ventilation, a continuous increase in end-tidal  $\text{CO}_2$  is a highly suspicious sign of the incompetency of either the inhalation or exhalation UDV. Measurable  $\text{CO}_2$  in the end-inspiratory air usually indicates an incompetent exhalation UDV, when soda lime exhaustion is ruled out. However, this does not commonly occur with an incompetent inhalation UDV.

If the exhalation UDV is incompetent, a fraction of the exhaled air retained in the exhalation limb is being returned to the patient throughout the inspiratory cycle. Consequently, the end-inspiratory air contains sufficient  $\text{CO}_2$  to be detected by a  $\text{CO}_2$  analyzer, even though end-tidal  $\text{CO}_2$  is not elevated.

If the inhalation UDV is incompetent, a fraction of the exhaled air that backs up into the  $\text{CO}_2$ -free inhalation limb is returned to the patient, mainly at the beginning of inspiration. Therefore, the  $\text{CO}_2$  concentration at the end of inspiration will be negligible unless the incompetency is excessive.

Other signs of an incompetent inhalation UDV observed by us include an apparent discrepancy between inspiratory and expiratory tidal volumes, and fogging in the connecting tubing between the heated humidifier and inhalation outlet. The latest model of the Dräger machine incorporates an optional warning

Table 1. Incompetent UDVs Found in Different Brands of Anesthesia Machines

Incomp UDVs	Ohio (n = 364)	Foregger (n = 155)	Dräger (n = 142)	Others (n = 54)	Total (n = 715)
Inhalation	32	12	5	6	55
Exhalation	13	16	0	3	32
Both	9	10	2	0	21
Total	54	38	7	9	108
%	15	25	5	16	15

device to detect reverse flow caused by an incompetent exhalation UDV.

A minor incompetency due to a dent on the annular seat can be detected by a blowing noise. As anesthetic gases rapidly pass through the small gap between the UDV and the dent on the annular seat, the gas flow becomes turbulent and a blowing noise is audible.

The volume fraction of rebreathing for a given minute ventilation depends upon the degree of incompetency. Even with the same degree of incompetency, small tidal volumes and rapid rates (commonly observed in anesthetized children and adult patients with spontaneous breathing), will greatly increase the fraction of rebreathing. In contrast, large tidal volumes with slow rates reduce the volume fraction of rebreathing. Therefore, the degree of  $\text{CO}_2$  retention caused by an incompetent UDV can vary. Because of the variability and difficulty in detecting incompetent valves, the incompetency may go unrecognized until serious hypercarbia develops.

Warping of the UDV is the most common cause of incompetency. The UDVs are horizontally seated on the sharp annular seat, and even slight warping of the UDV allows a large reverse flow. The Foregger valves showed the highest incidence of incompetency (25%), as compared with the Dräger valves (5%). The difference in frequency of incompetency between these two types of valves might be attributed to the material used. Conductive malleable rubber, the material used for the Foregger valve, seems more susceptible to warping by either mechanical forces or by natural deterioration. In contrast, mica, the material used for the Dräger valve, seems to resist warping.

Maintenance of UDVs is traditionally performed by technicians either by contract from the company or hired by the institution. The basic principle of the test involves demonstration of air flow against the direction of the UDV. The procedure we developed for testing incompetency is simple and sensitive, does not require extra equipment, and can be completed within 1 min. Therefore, testing can be performed at least once daily before administration of the first anesthesia of the day. We compared our method to a sim-

ilar test described by the Foregger Company (Foregger Anesthesia Circuit, Supplemental Operation Check, Puritan-Bennett Corp., Overland Park, KS. Printed 3/30/84). This test is more complicated and time consuming, requires detachment of the inhalation dome valve assembly, and application of 40 cm H<sub>2</sub>O positive pressure. Due to the complexity of the test, it loses practical applicability as a routine preoperative checkup procedure. Also, the positive pressure used in the test, 40 cm H<sub>2</sub>O, is not only beyond the range of normal airway pressure, but is also a high enough pressure to correct the slight warping of the UDV, resulting in a false-negative test.

The anesthesia machines found to have incompetent UDVs in our mail survey series (108 of 715 machines) could lead to serious hypercarbia, especially in children and spontaneously breathing adult patients. When hypercarbia occurs during anesthesia,

the incompetent UDV should be considered in the differential diagnosis. The clinical picture of some severe hypercarbic patients is similar to malignant hyperpyrexia. For the safety of anesthetized patients, the alarmingly high incidence of incompetent UDVs in the anesthesia circle system should be recognized, and steps taken to assure that incompetent UDVs are promptly identified and corrected.

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## Respiratory Insufficiency after Gastrostomy prior to Tracheoesophageal Fistula Repair

Mitchel Sošis, MD, PhD, and Michael Amoroso, MD

Attempts at one-stage surgical repair of congenital tracheoesophageal fistula (TEF) with distal esophageal atresia (DEA) in infants without prior insertion of a gastrostomy tube have resulted in catastrophic complications when intermittent positive pressure ventilation (IPPV) has been used. These include gastric rupture (1) or respiratory acidosis and cardiac arrest (2) due to gastric distension, impeding venous return and forcing the diaphragm to a more cephalad position.

In infants breathing spontaneously, a gastrostomy should be performed under local anesthesia prior to definitive repair of the fistula. This will prevent the aspiration of gastric contents (3,4). It should be undertaken as soon as possible after TEF has been diagnosed. Additional maneuvers to prevent aspiration include positioning of an endotracheal tube distal to the fistula (5) when the patient is intubated.

Survival rates of neonates with TEF and DEA appear to be most dependent on the degree of pulmonary compromise and prematurity (3). Neonates already dependent on positive pressure ventilation for survival may not benefit from gastrostomy tube insertion before ligation of the fistula. In fact, the respiratory status may even worsen in these cases. The following case report illustrates such a complication.

### Case Report

The patient was a 1300-gm premature infant. Ultrasound examination one month prior to delivery revealed a 25–28 week twin gestation. The infant showed increased echo in her right chest as well as dextrocardia. Apgar scores at birth were 4, 7, and 9 at 1, 5 and 10 minutes, respectively. She was intubated at 1 min for persistent bradycardia and cyanosis. A nasogastric tube could not be passed at this time.

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An initial radiograph revealed gas in the gastrointestinal tract and dextrocardia. The right lung was not visualized, and the left lung field showed changes consistent with hyaline membrane disease (HMD). No gross vertebral abnormalities were noted, and the nasogastric tube was seen coiled in the upper esophagus.

A presumptive diagnosis of TEF with DEA, hypoplasia of the right lung, dextrocardia, and HMD was made. Due to severe pulmonary insufficiency, she was maintained on positive pressure ventilation with intermittent mandatory ventilation at 40 breaths/min.  $FI_{O_2}$  was 0.3, peak inspiratory pressure was 15 cm  $H_2O$ . Her abdomen was distended.

Surgery for gastrostomy tube placement was scheduled for her second day of life. Hyperalimentation was begun, and peripheral intravenous and umbilical artery catheters were placed, as were a transcutaneous  $PO_2$  monitor ( $TCPO_2$ ) and a rectal thermistor probe. A stethoscope was positioned in the left axilla, and good breath sounds were heard. Anesthesia was induced with 3  $\mu g/kg$  fentanyl. Muscle relaxation was provided by 0.1 mg/kg pancuronium. Ventilation was controlled, and her abdomen remained nondistended.

Surgery was uneventful until the stomach was opened and a massive gas leak made axillary breath sounds impossible to hear.  $TCPO_2$  readings decreased to 30–50 mm Hg within 1 min, despite increasing  $FI_{O_2}$  to 1.0 and hyperventilation. An umbilical artery blood gas sample at this time showed pH 7.02;  $PCO_2$ , 81 mm Hg; and  $PO_2$ , 41 mm Hg. Sodium bicarbonate was administered, and a gastrostomy tube was quickly inserted. Attempts to clamp the tube resulted in gastric distention. The abdomen was quickly closed.

Over the next few hours much difficulty was encountered compensating for the gas leak through the gastrostomy tube. Her condition did not improve until the tube was placed under 25 cm of water. Ventilation gradually improved over the next several hours. Bubbling from the water-sealed tube subsided, and the abdomen remained nondistended.



Peak airway pressure, initially 15 cm H<sub>2</sub>O prior to surgery, decreased to approximately 5 cm H<sub>2</sub>O when the stomach was opened. It increased to approximately 25 cm H<sub>2</sub>O after the water seal was begun and declined to approximately 20 cm H<sub>2</sub>O when the patient was weaned from the water seal on the second postoperative day.

By the eighth postoperative day, she was weaned from the ventilator, given 25% oxygen by tent, and extubated. Definitive repair was planned for a later date, after the infant's weight had reached 1800 g. Persistent bouts of aspiration, despite the presence of the gastrostomy tube, precluded such delay. The TEF was ligated on the twenty-second day of life. She tolerated this procedure well and was extubated 8 days later. Feeding through the gastrostomy tube was begun, and further bouts of aspiration were eliminated. At present she remains stable and awaits esophageal anastomosis after further nutritional buildup.

## Discussion

TEF with associated DEA in the neonate is rarely an isolated anomaly (3,4). Vertebral and cardiac anomalies, imperforate anus, renal agenesis, and radial abnormalities such as radial artery agenesis and polydactyly, are some of the associated problems described. However, the two most important associated anomalies affecting survival rates of these infants are the presence of significant pulmonary disease and prematurity (3,4,6).

Neonates born with congenital TEF with DEA and associated pulmonary hypoplasia or agenesis represent a special subset of individuals who are at extremely high risk during surgical intervention. Breveton and Richwood describe eleven cases of premature infants with TEF and DEA with associated pulmonary agenesis or hypoplasia (6). Most died before the age of 6 yr, whereas in the absence of significant pulmonary complications survival rate approaches 100% (3,4).

Under normal circumstances, surgical repair of congenital TEF in the premature neonate ideally is not attempted until a weight of at least 1800 g has been achieved by hyperalimentation (3). Such a delay is only feasible if the infant's course is not complicated by repeated aspiration of gastric contents (3,4). Traditionally this has been one of the major reasons for inserting a gastrostomy tube prior to surgical repair.

Furthermore, Holder and Ashcroft (7) point out that inserting a gastrostomy tube in these infants also serves to put the esophagus at rest after the anasto-

mosis and could be used as a feeding tube after repair. Myers and Love noted the function of the gastrostomy tube to include prevention of gastric distention during definitive repair of TEF and esophageal anastomosis (8). However, there is only one report (9) in the literature describing difficulties encountered in gastrostomy tube placement, especially in premature infants with HMD and pulmonary hypoplasia or agenesis on IPPV. General anesthesia in addition to surgical retractors could conspire to decrease lung compliance. However, the ventilatory leak in this patient continued to be a management problem, even after retractors were removed.

Salem and Wong suggested that careful positioning of the endotracheal tube might occlude the TEF (10). The tube should be advanced to the level of the carina, or even into the right mainstem bronchus if possible, then withdrawn 0.5–1.0 cm until breath sounds are heard bilaterally. This was also not feasible in this infant because there was no right lung. Left mainstem intubation was technically impossible. Several attempts resulted in severe cyanosis and bradycardia.

The massive air leak subsided only after placing the gastrostomy tube under 25 cm of water without suction. This particular maneuver has not been reported in these cases. It allowed us to stabilize her ventilation and correct acid-base abnormalities.

The reports of complications listed above (1,2) in patients with TEA and DEA were the result of IPPV being instituted prior to the gastrostomy. We are aware of no complications of this type when a gastrostomy is placed with the patient under local anesthesia and IPPV is not used. When such a patient is already ventilator dependent, this report should serve as a warning that gastrostomy placement to prevent aspiration may lead to deterioration of respiratory status. This may necessitate the immediate definitive closure of the fistula, even when it might have been desirable for the closure to be done later, when a more optimal state of nutrition had been achieved (3). Also of interest is the fact that this infant had bouts of aspiration even after the gastrostomy.

We have presented a case of a premature infant with TEF and DEA, who was ventilator dependent, and in whom placement of a gastrostomy tube while she was under general anesthesia prior to definitive repair caused such a life threatening diversion of the inspired gases away from the lungs.

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## Letters to the Editor

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### Sensitive Measures of Outcome

To the Editor:

The editorial by Dr. Roizen entitled "But what does it do to outcome?" (*Anesth Analg* 1984;63:789-90) was a provocative piece. We agree with Dr. Roizen that it is important to examine outcome, but we believe that the most crucial task is to identify and focus on discriminant outcome variables rather than easily measured but relatively gross measures such as mortality. For example, attempts to detect differences in outcome in terms of mortality (incidence about 1%) or infarction (incidence about 6%) after coronary artery bypass grafting (CABG) surgery in patients randomized to two different anesthetic techniques, while laudable, would represent an almost hopeless task given that in well conducted CABG operations the mortality and infarction rates are already so low. Thus in our opinion, the challenge to anesthesia investigators is not to design massive multicenter studies with all their inherent problems, as Dr. Roizen suggests, but to develop sensitive scientific outcome-related measures that discriminate between "better" anesthetic techniques. An example of clinical investigational techniques presently used at our institution for this purpose are ultrasonic dimension transducers and intracavitary micromanometers that are more sensitive indices of ventricular function than cardiac output or pulmonary artery wedge pressure. These techniques might differentiate anesthetic effects on preservation of ventricular contractility (1,2) and diastolic compliance (3), which are two specific outcome-related measures. Funding for development of such sensitive outcome measures would be a much more prudent use of federal monies than large multicenter studies that are difficult to control and by necessity examine only gross outcome variables. In summary, it is indeed fortunate that in most procedures we have reached a level of anesthesia and surgical care where simple measures of morbid events are unlikely to help differentiate anesthetic techniques. Let us direct our attention and resources to the development of more sensitive outcome-related indices that may elucidate the influence of anesthetic techniques on surgical outcome.

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### In Response:

One cannot argue with Reves et al. that performing outcome studies is greatly facilitated by a high frequency event in a single institution. That is why I have concentrated my clinical research efforts on anesthesia for major vascular surgery. Cardiovascular morbidity and mortality is 3- to 5-fold greater after major vascular surgery than after CABG (1).

However, I believe our specialty has defined outcome variables in CABG surgery that occur with high enough frequency to be studied. Neurologic dysfunction follows CABG in 20% of patients (2). Slogoff and Keats (3) report over a 25% incidence of 2-lead ECG evidence of myocardial ischemia in their CABG population. Roy and colleagues found over a 35% incidence of myocardial ischemia during noncardiac surgical procedures (4). Reves' own group (5) employs intracavitary micrometers to examine cardiac function (but I take exception to calling changes in global contractility an alteration in an outcome variable in most situations). New relatively noninvasive devices reveal the true incidence of myocardial ischemia: Kotrly and colleagues (6) have reported on an ST-T segment trend monitor; Smith and colleagues (7) have presented data that ischemic changes were four times more frequently detected by 2-D transesophageal echocardiography than by 7-lead ECG in a high risk population. These studies (3,7) indicate that a high frequency event (intraoperative myocardial ischemia) predicts the low frequency event of postoperative myocardial infarction. Thus we may be nearing the time when frequent intermediate process variables that predict outcome variables can be studied relatively noninvasively.

But even with a relatively high frequency event, it is difficult to study large enough populations at one center to tell whether a treatment is beneficial. For instance, if preoperative hypertension is associated with 20% morbidity, and preoperative treatment of hypertension reduces that to 10%, you would have to study over 450 patients to have an 80% chance of finding that difference (8).

Yes, our specialty needs high frequency intermediate outcome variables, and we may already have them. However, we also need good multicenter outcome studies (Do not condemn all multicenter studies because one may not have been ideally designed). Perhaps the greatest medical advance of the last two decades occurred because of a multicenter study: the VA cooperative study (9) that showed a benefit from treatment of hypertension. This multicenter study undoubtedly is responsible for a significant portion of the 40% decline in stroke rate and the 25% decline in myocardial infarction and CHF death rates this country has experienced since 1970.

I believe our specialty needs both types of investigations and investigators (like Reves and colleagues) with the imagination and drive to see their work to fruition.

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## Anesthesia and Analgesia are Mediated by Different Mechanisms

To the Editor:

In their paper on molecular mechanisms of anesthesia, Ueda and Kamaya, in discussing receptor theories, clearly distinguish between local and general anesthesia (1). However, they then lump together the terms anesthesia and analgesia, without clearly making a distinction between these two very different states. These authors cite various workers who have provided evidence for the hypothesis that the endogenous opioid system (EOS) is concerned with the production of anesthesia (2), but close inspection of these references reveal that, in fact the investigators referred to studied analgesic states, or substances that quite clearly produce analgesia before producing anesthesia (3,4).

Ueda and Kamaya then go on to quote work in which the inability of opioid antagonists to reverse *anesthesia* is taken as support of the premise that opioid receptors are not directly involved in the mechanism of action of anesthetics (1). While it is possible that *anesthesia* does not necessarily require the involvement of the EOS, this is not so for *analgesia*. Of course, this does not imply that all analgesics have their primary effect via EOS mediation; for instance the analgesia produced by non-steroid analgesic agents appears to involve prostoglandin synthetase inhibition mainly at the periphery (8). There is now considerable evidence that the analgesic effects of opiate and opioid anesthetics such as morphine, fentanyl, and others are mediated via the EOS (5). This statement is also true for the analgesic effects of nitrous oxide (6,7).

It is thus of the utmost importance to dissociate the terms *analgesia* and *anesthesia* when describing the mechanism of action of these two completely different states.

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In Response:

We cannot agree more. Dr. Gillman must have misread the article. In our review, we have explicitly stated that "the profound analgesia produced by large doses of morphine and its analogs is not the same as the state of general anesthesia . . . The state of indifference induced by narcotics must be differentiated from the state of true anesthesia."

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# A Guide for Authors

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You CH, Lee KY, Chey RY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. *Gastroenterology* 1980;79:311-4.
2. *Corporate Author*  
The Royal Marsden Hospital Bone-Marrow Transplantation Team. Failure of syngeneic bone-marrow graft without preconditioning in post-hepatitis marrow aplasia. *Lancet* 1977;2: 242-4.
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Anonymous. Coffee drinking and cancer of the pancreas (Editorial). *Br Med J* 1981;283:628.
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Mastri AR. Neuropathy of diabetic neurogenic bladder. *Ann Intern Med* 1980;92(2 Pt 2):316-8.  
Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan (Abstract). *Blood* 1979;54(suppl 1):26a.
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Seaman WB. The case of the pancreatic pseudocyst. *Hosp Pract* 1981;16(Sep):24-5.

#### Books and Other Monographs:

6. *Personal Author(s)*  
Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.

7. *Editor, Compiler, Chairman as Author*  
Dausset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.
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Ranofsky AL. Surgical operations in short-stay hospitals: United States—1975. Hyattsville, Maryland: National Center for Health Statistics, 1978; DHEW publication no. (PHS) 78-1785. (Vital and health statistics; series 13; no. 34).
12. *Dissertation or Thesis*  
Cairns RB. Infrared spectroscopic studies of solid oxygen (Dissertation). Berkeley, California: University of California, 1965. 156 pp.

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- ☐ Letters, numbers, and symbols should be clear and even throughout and of sufficient size that, when reduced for publication, each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves.
- ☐ Each figure must have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount

them on cardboard, or scratch or mar them by using paper clips. Do not bend figures.

- ☐ Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with the background.
- ☐ If photographs of patients are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.
- ☐ Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, regardless of authorship or publisher, except for documents in the public domain.
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#### Legends for Illustration

- ☐ Type legends for illustrations double spaced starting on a separate page, with arabic numerals corresponding to the illustrations.
- ☐ When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain internal scale and identify method of staining in photomicrographs.

#### Abbreviations

- ☐ The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement. Avoid abbreviations in the title.

- ☐ Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

- ☐ Consult the following sources for abbreviations:

1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and
2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

#### Ethical Principles

- ☐ When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or are in accord with the Helsinki Declaration of 1975.
- ☐ When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed.

#### Exclusive Publication Statement

- ☐ The principal author of all materials submitted for publication (except letters to the editor) must include in a covering letter a statement to the effect that none of the material in this manuscript has been published previously nor is any of this material currently under consideration for publication elsewhere.
- ☐ Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.



# ANESTHESIA RECORD

SUMMARY OF PRE OPERATIVE FINDINGS SEX **F** RACE AGE **40** WEIGHT **52.5 kg** HABITUS  
 BP **128/90** TPR **37/80/** HGB/HCT **12.7/37.6** URINALYSIS **1.09** OTHER LAB DATA  
 FOOD INTAKE **NPO**

PHYSICAL STATUS **II**

PRE OPER DIAGNOSIS **Malignant Melanoma**

PRE OP VISIT **Yes**

ANESTHESIOLOGIST

SURGEON

POST OPER DIAGNOSIS

**Same**

PREPARED

**Wide excision of tumor & transposition of sartorius (R) groin dissection**

PREMEDICATION

TIME

DRUG AND ROUTE

EFFECT

INDUCTION AGENTS

AGENT

DOSE OR METHOD

MAINTENANCE AGENTS

AGENT

DOSE OR METHOD

0830

Diazepam

7.5 mg IV

0830

Diazepam

7.5 mg IV

0830

Sufentanil

10 µg IV

0830

Sufentanil

10 µg IV

0830

Pancuronium

3.5 mg IV

0830

Sufentanil

10 µg IV

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*...More Predictable Control  
from Induction through Recovery*

## **COMPARED WITH ISOFLURANE<sup>\*1,2</sup>**

- Superior hemodynamic stability
- Shorter recovery times
- Better maintenance of postoperative analgesia
- Lower total cost per procedure

\*In a comparative study<sup>1,2</sup> of patients undergoing major orthopedic surgery who received either SUFENTA-N<sub>2</sub>O (n=10) or isoflurane-N<sub>2</sub>O (n=10).

1. Scientific Exhibit, Sufentanil vs. Isoflurane in Major Orthopedic Procedures (Fahmy NR, Principal Investigator), March 1983.

2. Fahmy NR, Beemer GH, Roberts JT: Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

## **COMPARED WITH FENTANYL<sup>3,4</sup>**

- Smoother, more rapid induction
- When given before intubation, reduces hypertension and tachycardia
- Promotes fast, comfortable recovery
- More effective blocking of catecholamine response to surgery
- Superior intraoperative hemodynamic stability
- Smaller volume of injection
- Lower total cost per procedure

3. Smith NT, Dec-Silver H, Harrison WK, et al: ASA Abstract, *Anesthesiology* (Suppl) 57: A291, 1982.

4. Flacke JW, Bloor BC, Flacke WE, et al: Comparative Effects of Sufentanil and Fentanyl Versus Meperidine and Morphine in Balanced Anesthesia. Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

For full Prescribing Information, please see next page.

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PHARMACEUTICA**



# SUFENTA® (sufentanil citrate) Injection

**CAUTION:** Federal Law Prohibits Dispensing Without Prescription

## DESCRIPTION

SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (11).

SUFENTA is a sterile, preservative-free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-7.5.

## CLINICAL PHARMACOLOGY

SUFENTA is an opioid analgesic. SUFENTA is approximately 5 to 7 times as potent as fentanyl. (Dosage requirements for equianalgesic effect will be 1/5-1/7 those of fentanyl on a mg/kg basis.) At doses of up to 8 µg/kg, SUFENTA provides profound analgesia, at doses ≥8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 0.72 minutes, redistribution of 13.7 minutes and an elimination half-life of 148 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl, at dosages of >2-6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of fentanyl.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

## INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated:

as an analgesic adjunct at dosages of up to 8 µg/kg in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

## CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

## WARNINGS

**SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthesia and management of the respiratory effects of potent opioids.**

**An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.**

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

## PRECAUTIONS

The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Drug Interactions: An additive effect with SUFENTA may be exhibited in patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

**Pregnancy Category C:** SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

**Animal Toxicology:** The intravenous LD<sub>50</sub> of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

## ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%); hypertension (3%); chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia  
Gastrointestinal: nausea, vomiting  
Respiratory: apnea, postoperative respiratory depression, bronchospasm  
Dermatological: itching  
Central Nervous System: chills  
Miscellaneous: intraoperative muscle movement

## DRUG ABUSE AND DEPENDENCE

SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

## OVERDOSAGE

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD<sub>50</sub> of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD<sub>50</sub>s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

## DOSAGE AND ADMINISTRATION

The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

**Usage in Children:** For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 2550 µg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

**Premedication:** The selection of preanesthetic medications should be based upon the needs of the individual patient.

**Neuromuscular Blocking Agents:** The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART	
TOTAL DOSAGE	MAINTENANCE DOSAGE
<b>1-2 µg/kg:</b> administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	<b>10-25 µg (0.2-0.5 ml):</b> as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.
<b>2-8 µg/kg:</b> administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	<b>25-50 µg (0.5-1 ml):</b> as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
<b>8-30 µg/kg:</b> (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Post-operative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	<b>25-50 µg (0.5-1 ml):</b> as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

## HOW SUPPLIED

SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

NDC 50458-050-01 50 µg/ml, 1 ml ampoules in packages of 10  
NDC 50458-050-02 50 µg/ml, 2 ml ampoules in packages of 10  
NDC 50458-050-05 50 µg/ml, 5 ml ampoules in packages of 10

Protect from light. Store at room temperature.



**JANSSEN**  
PHARMACEUTICA

Piscataway, N.J. 08854

U.S. Patent No. 3,998,834

7618501-M

May 1984, June 1984



## Introducing STRAPEZE™

While others slip and slide all over the place, we've made a name for ourselves by staying put.

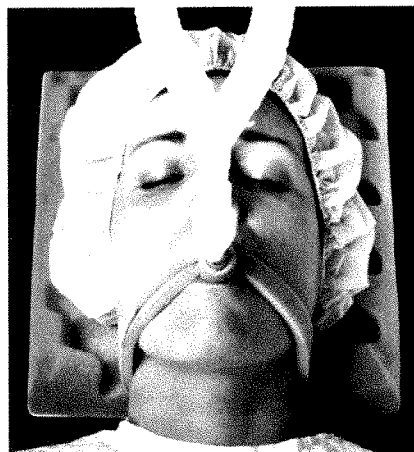
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Now you can forget about accidental extubations or bronchial intubations. STRAPEZE ensures precise and positive positioning of the tube. Where you put it, is where it stays. Which means the tube won't pull out, and it won't push down. Needless to say, such assurances can be a lifesaver.

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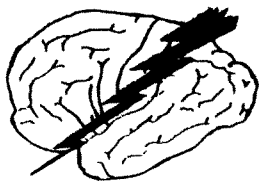
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**PAVULON™**  
(pancuronium bromide injection)

**BRIEF SUMMARY**  
(Please consult package insert for full prescribing information.)

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS  
FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS

**ACTIONS:** Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane, and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin, and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

**CONTRAINDICATIONS:** Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

**WARNINGS:** PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

**USAGE IN PREGNANCY:** The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

**PRECAUTIONS:** Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

**ADVERSE REACTIONS:** Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

**DRUG INTERACTION:** The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

**DOSAGE AND ADMINISTRATION:** Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

**CAUTION:** Federal law prohibits dispensing without prescription.

#### HOW SUPPLIED:

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10 ml vials—1 mg./ml.—boxes of 25, NDC #0052-0443-25

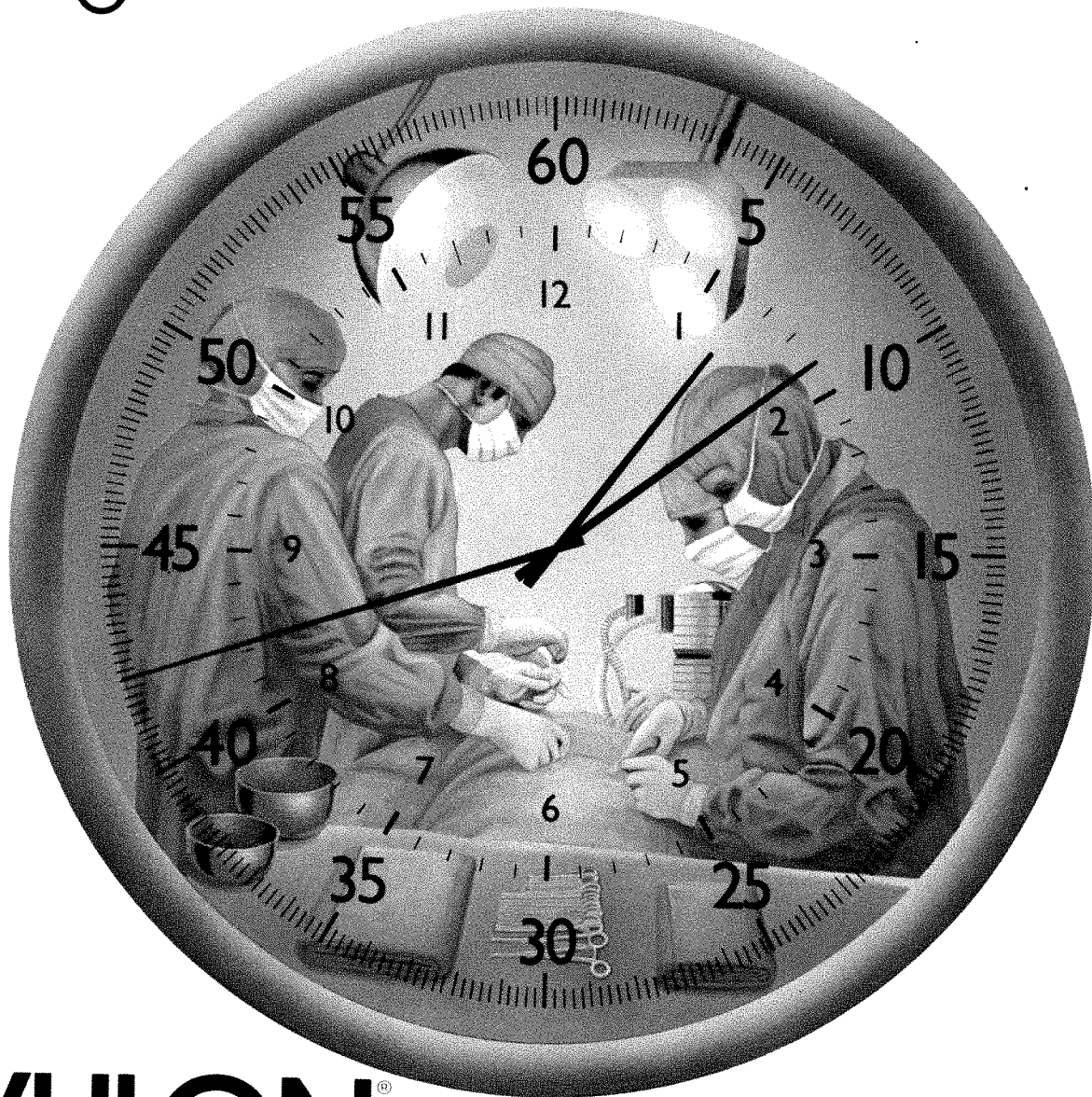


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Please see preceding page for brief summary of prescribing information.

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(pyridostigmine  
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when compared to neostigmine

- ☐ Clinically fewer side effects
- ☐ Significantly lower degree and incidence of:
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  - 2) Salivation
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- ☐ Wide margin of safety<sup>1,2</sup>



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## Regonol (pyridostigmine bromide injection USP)

**BRIEF SUMMARY**—(Please consult full package insert enclosed in every package, before using Regonol)

**INDICATIONS**—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

**CONTRAINDICATIONS**—Known hypersensitivity to anticholinesterase agents, intestinal and urinary obstructions of mechanical type.

**WARNINGS**—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and anti-shock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

**Use in Pregnancy**—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

**ADVERSE REACTIONS**—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

**DOSAGE AND ADMINISTRATION**—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg/kg. Usually 10 or 20 mg of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

**HOW SUPPLIED**—Regonol is available in:  
5 mg./ml. 2 ml. ampuls—boxes of 25—NDC-0052-0460-02  
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### REFERENCES:

1. Gyermek L. Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. 1. The effects of glycopyrrolate and pyridostigmine. *Curr Ther Res* 18:377-386, 1975.
2. Ravin MB. Pyridostigmine as an antagonist of d-tubocurarine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg—Curr Res* 54:317-321, 1975.



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# Anesthesia and Analgesia

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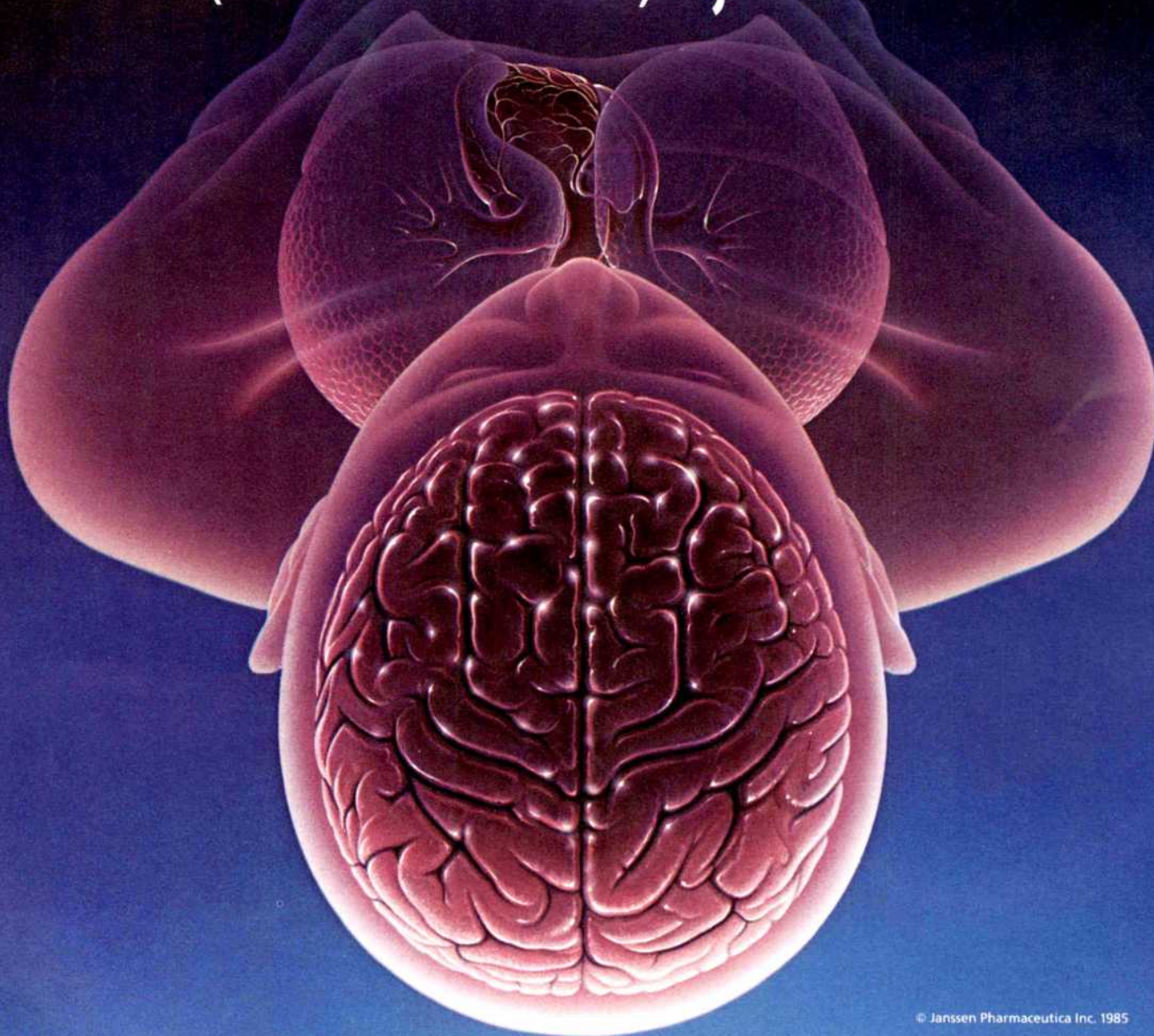
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# ANESTHESIA RECORD

SUMMARY OF PRE-OPERATIVE FINDINGS SEX *F* RACE AGE *40* WEIGHT *52.5 kg* HABITUS  
 BP *128/90* TPR *37/80/* HGB HCT URINALYSIS *1.09* OTHER LAB DATA TEETH *upper & partial lower denture*  
*12.7 / 37.6* *p 45.0* FOOD INTAKE *NPO*  
*+ ketones*  
 PHYSICAL STATUS *II* PRE-OPER. DIAGNOSIS *Malignant Melanoma* PRE-OP. VISIT *Yes*

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1. Scientific Exhibit, Sufentanil vs. Isoflurane in Major Orthopedic Procedures (Fahmy NR, Principal Investigator), March 1983.

2. Fahmy NR, Beemer GH, Roberts JT: Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

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3. Smith NT, Dec-Silver H, Harrison WK, et al: ASA Abstract, *Anesthesiology* (Suppl) 57: A291, 1982.

4. Flacke JW, Bloor BC, Flacke WE, et al: Comparative Effects of Sufentanil and Fentanyl Versus Meperidine and Morphine in Balanced Anesthesia. Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

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The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 0.72 minutes, redistribution of 137 minutes and an elimination half-life of 148 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 6-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥ 8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of fentanyl.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

## INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated:

as an analgesic adjunct at dosages of up to 8 µg/kg in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

## CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

## WARNINGS

**SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.**

**An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.**

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg; 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or; 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

## PRECAUTIONS

The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Drug Interactions: An additive effect with SUFENTA may be exhibited in patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

**Pregnancy Category C:** SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

**Animal Toxicology:** The intravenous LD<sub>50</sub> of SUFENTA is 16.8 to 18.0 mg/kg in mice, 118 to 130 mg/kg in guinea pigs and 101 to 135 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

## ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia  
Gastrointestinal: nausea, vomiting  
Respiratory: apnea, postoperative respiratory depression, bronchospasm  
Dermatological: itching  
Central Nervous System: chills  
Miscellaneous: intraoperative muscle movement

## DRUG ABUSE AND DEPENDENCE

SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

## OVERDOSAGE

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD<sub>50</sub> of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD<sub>50</sub>s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist.

Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

## DOSAGE AND ADMINISTRATION

The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥ 8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

**Usage in Children:** For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

**Premedication:** The selection of preanesthetic medications should be based upon the needs of the individual patient.

**Neuromuscular Blocking Agents:** The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART	
TOTAL DOSAGE	MAINTENANCE DOSAGE
<b>1-2 µg/kg:</b> administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	<b>10-25 µg (0.2-0.5 ml):</b> as needed when movement and/or changes in vital signs indicate surgical stress or lightening of anesthesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.
<b>2-8 µg/kg:</b> administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	<b>25-50 µg (0.5-1 ml):</b> as determined by changes in vital signs that indicate stress or lightening of anesthesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
<b>8-30 µg/kg:</b> (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥ 8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Post-operative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	<b>25-50 µg (0.5-1 ml):</b> as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

## HOW SUPPLIED

SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

NDC 50458-050-01 50 µg/ml, 1 ml ampoules in packages of 10  
NDC 50458-050-02 50 µg/ml, 2 ml ampoules in packages of 10  
NDC 50458-050-05 50 µg/ml, 5 ml ampoules in packages of 10

Protect from light. Store at room temperature.



**JANSSEN**  
PHARMACEUTICA

Piscataway, N.J. 08854

U.S. Patent No. 3,998,834

7618501M

May 1984, June 1984



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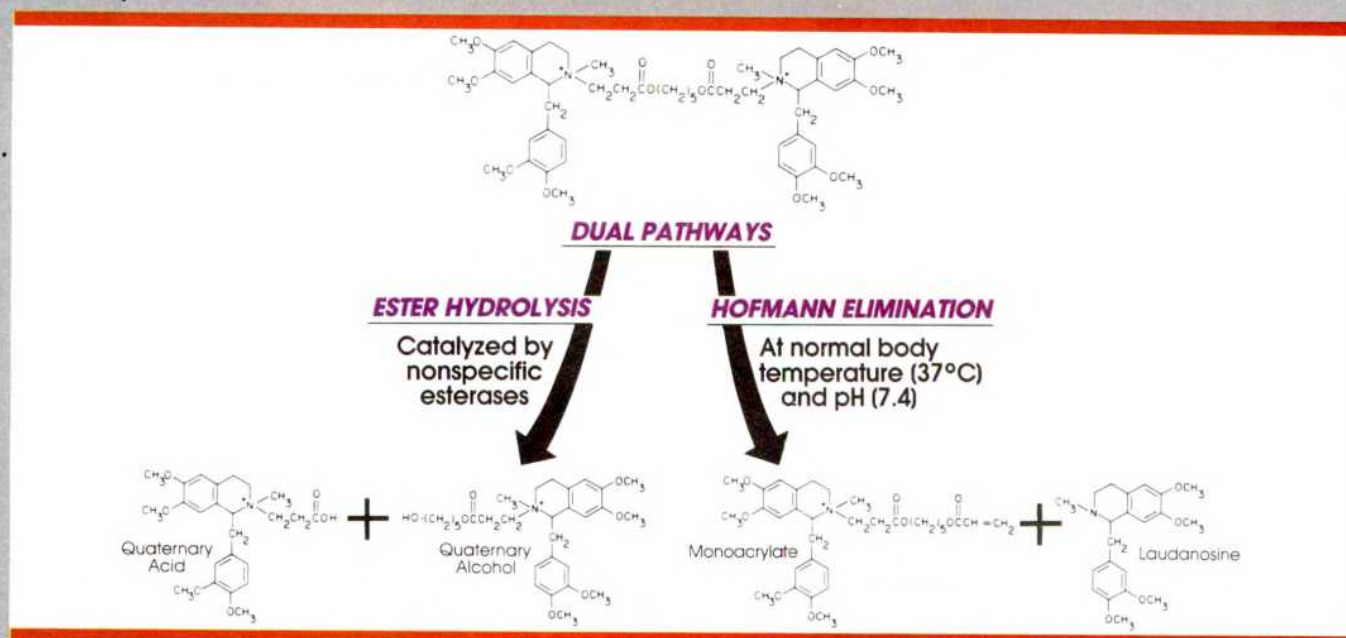
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EFFECTS AND GREATER  
CONTROLLABILITY**

**NO MIXING NEEDED!**





# UNIQUE METABOLISM PROVIDES BETTER PREDICTABILITY, ALLOWING BETTER CONTROL



□ *Tracrium® Injection (atracurium besylate)* is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:

① *Hofmann elimination*—a nonenzymatic process that occurs at physiologic temperature and pH

② *Ester hydrolysis*—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required

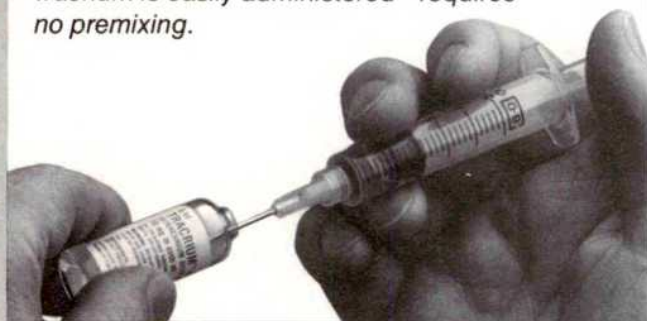
These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."<sup>1</sup>

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."<sup>2</sup>

## Convenient and Ready to Use

Tracrium is easily administered—requires no premixing.

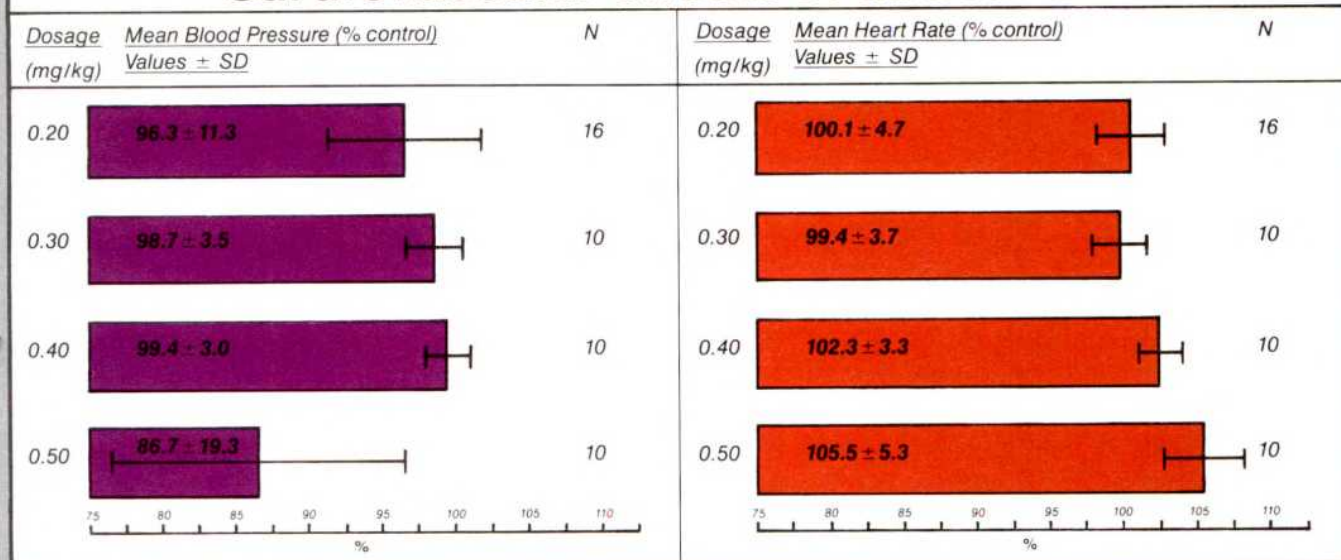




## Few Cardiovascular Effects at Recommended Dosages

☐ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.

### Cardiovascular effects of atracurium



Adapted from Basta et al.<sup>3</sup>

## No Cumulative Effects Upon Recovery, After Multiple Doses

☐ Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time

☐ Once recovery begins, it is relatively rapid and independent of dose

☐ This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."<sup>1</sup>

## Minimal Histamine Release

☐ Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine

☐ Clinically significant histamine release occurs well within the clinical dosage range (at ED<sub>95</sub>) for curare, at the upper limits of the clinical dosage range (at 2  $\times$  ED<sub>95</sub>) for metocurine and outside the clinical dosage range (at 3  $\times$  ED<sub>95</sub>) for atracurium<sup>4</sup>

☐ The lack of hemodynamic changes due to Tracrium suggests minimal histamine release

Please see brief summary of prescribing information on the following page.

#### REFERENCES:

1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. *Seminars in Anesthesia* 1982; 1:57-62.
2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. *Anesth Analg* 1982; 61:730-734.
3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. *Anesth Analg* 1982; 61:723-729.
4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. *Anesthesiology* 1982; 57:A261.

**TRACRIUM® INJECTION**  
(atracurium besylate)



# TRACRIUM® INJECTION

(atracurium besylate)

**DESCRIPTION:** Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

**INDICATIONS AND USAGE:** Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it.

**WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebation. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

## PRECAUTIONS:

**General:** Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Pregnancy: Teratogenic Effects:** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 2 years have not been established.

**ADVERSE REACTIONS:** Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

In the United Kingdom, where Tracrium has been marketed since December, 1982, the most frequent adverse reactions reported in association with the use of Tracrium are cutaneous histamine-like reactions, bronchospasm, and bradycardia. These have been reported to occur in about one in 10,000 patients. Less frequent adverse reactions are hypotension, heart arrest, tachycardia, cyanosis, and apnea, which have been reported to occur in approximately one in 100,000 patients.

**DOSAGE AND ADMINISTRATION:** Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

**HOW SUPPLIED:** Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4179507

Printed in U.S.A.

You can learn more about  
**TRACRIUM® INJECTION**  
(atracurium besylate)

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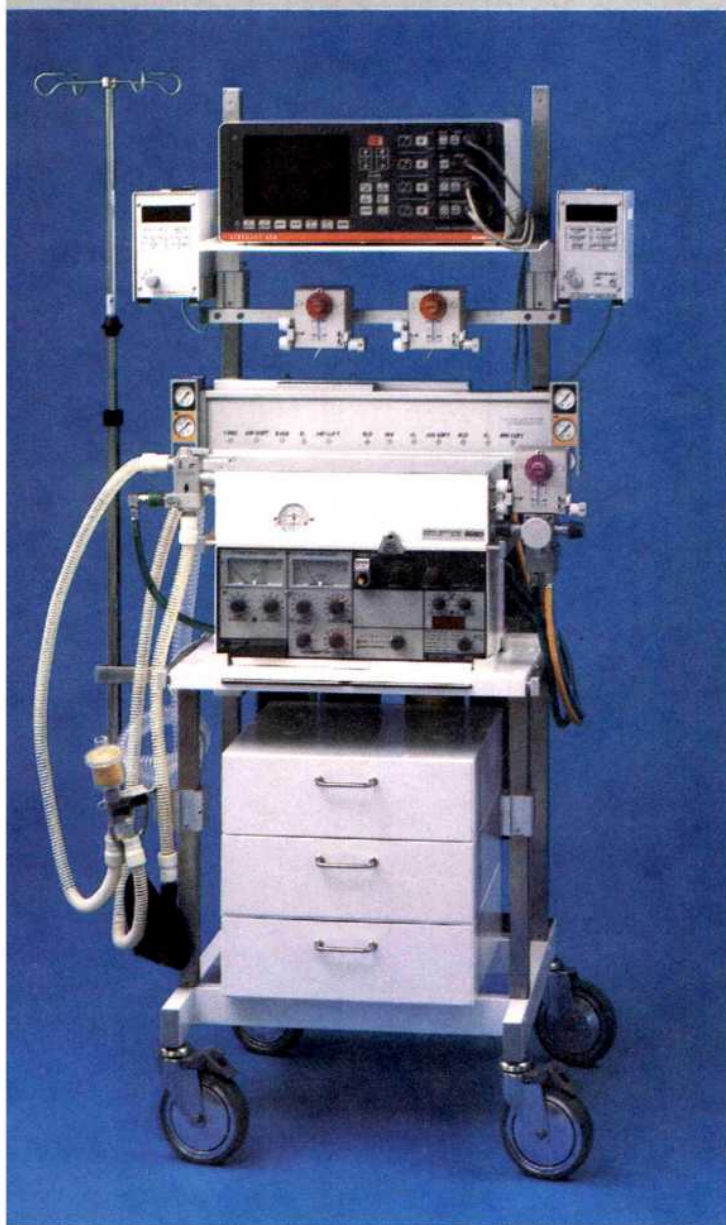
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## INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

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The B.B. Sankey Anesthesia Advancement Award has been established to expand upon and replace the IARS Research Award. This new award is intended to foster investigative efforts in the fields of anesthesia research, clinical care, education and administration.

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- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office not later than December 16, 1985.
- The official application form for the award must be used. This form, as well as the guidelines for applicants, is available on request to:

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bupivacaine HCl, USP, 0.75%  
with dextrose, USP, 8.25% injection

## PLEASE CONSULT FULL PRESCRIBING INFORMATION: A SUMMARY FOLLOWS:

**CONTRAINDICATIONS:** MARCAINE Spinal is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type. The following conditions preclude the use of spinal anesthesia: (1) Severe hemorrhage, severe hypotension, or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output. (2) Local infection at the site of proposed lumbar puncture. (3) Septicemia.

**WARNINGS:** LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS and PRECAUTIONS.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Spinal anesthetics should not be injected during uterine contractions, because spinal fluid current may carry the drug further cephalad than desired.

A free flow of cerebrospinal fluid while performing spinal anesthesia indicates entry into the subarachnoid space. Aspiration should be performed before the anesthetic is injected to confirm entry into the subarachnoid space and to avoid intravascular injection.

MARCAINE solutions containing epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because severe, persistent hypertension may occur. MARCAINE solutions containing a vasoconstrictor such as epinephrine should be used cautiously in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the tricyclic or imipramine types, because severe prolonged hypertension may result.

Administration of MARCAINE to patients younger than 18 years is not recommended, nor is the mixing or the prior or concurrent use of any other local anesthetic with MARCAINE because of insufficient data on the clinical use of such mixtures.

**PRECAUTIONS: General:** The safety and effectiveness of spinal anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS.) The patients should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used. Aspiration for blood should be performed before injection and injection should be made slowly. Tolerance varies with the status of the patient. Elderly patients and acutely ill patients may require reduced doses. Reduced doses may also be indicated in patients with increased intra-abdominal pressure (including obstetrical patients), if otherwise suitable for spinal anesthesia.

Cardiovascular and respiratory vital signs and the patient's state of consciousness after local anesthetic injection should be constantly and carefully monitored. Restlessness, anxiety, incoherent speech, light-headedness, numbness, and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Spinal anesthetics should be used cautiously in patients with severe disturbances of cardiac rhythm, shock or heart block.

Sympathetic blockade during spinal anesthesia may result in peripheral vasodilation and hypotension, the extent depending on the number of dermatomes blocked. Blood pressure should be carefully monitored especially in the early phases of anesthesia. Hypotension may be controlled by vasoconstrictors in dosages depending on the severity of hypotension and response of treatment. The level of anesthesia should also be carefully monitored because it is not always controllable in these techniques.

Because the liver metabolizes amide-type local anesthetics such as MARCAINE, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used cautiously in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. However, dosage recommendations for spinal anesthesia are much lower than those in other major blocks, most experience regarding hepatic and cardiovascular disease dose-related toxicity is derived from these other major blocks.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are used in patients during or following the administration of potent inhalation agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be considered.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. It is not known whether amide-type local anesthetics trigger this reaction, and since the need for supplemental general anesthesia cannot be predicted in advance, a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome depends on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene. (Consult dantrolene sodium package insert before use.)

The following conditions may preclude the use of spinal anesthesia, depending on the physician's evaluation of the situation and ability to deal with possible complications or complaints: (1) Preexisting diseases of the central nervous system, such as those resulting from pernicious anemia, poliomyelitis, syphilis, tumor. (2) Hematological disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage. (3) Chronic backache and preoperative headache. (4) Hypotension and hypertension. (5) Technical problems (persistent paresthesias or bloody tap). (6) Arthritis or spinal deformity. (7) Extremes of age. (8) Psychosis or other causes of poor cooperation by the patient.

**Information for Patients:** Patients should be informed that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the MARCAINE Spinal package insert.

**Clinically Significant Drug Interactions:** Local anesthetic solutions containing epinephrine or norepinephrine administered to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided but, when necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term studies in animals of most local anesthetics including bupivacaine to evaluate carcinogenic potential have not been conducted. Mutagenic potential or the effect on fertility have not been determined. There is no evidence from human data that MARCAINE Spinal may be carcinogenic, or mutagenic or that it impairs fertility.

**Pregnancy Category C:** Data based on pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered in doses comparable to 230 and 130 times respectively the maximum recommended human spinal dose. There are no adequate and well-controlled studies in pregnant women of bupivacaine's effect on the developing fetus. Bupivacaine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This does not exclude the use of MARCAINE Spinal at term for obstetrical anesthesia. (See Labor and Delivery.) **Labor and Delivery:** Spinal anesthesia has a recognized use during labor and delivery. Bupivacaine hydrochloride, when administered properly, via the epidural route in doses 10 to 12 times the amount used in spinal anesthesia has been used for obstetrical analgesia and anesthesia without evidence of adverse effects on the fetus.

Regional anesthesia has produced maternal hypotension. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent blood pressure drop. The fetal heart rate should be monitored continuously and electronic fetal monitoring is highly advisable.

It is extremely important to avoid aortocaval compression by the gravid uterus during administrations of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and the gravid uterus displaced to the left.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. Obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may result in diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

Cardiac arrest has been reported during use of MARCAINE 0.75% solution for epidural anesthesia in obstetrical patients. The MARCAINE hydrochloride package insert for epidural, nerve block, etc. discusses this problem. These cases are compatible with systemic toxicity following unintended intravascu-

lar injection of the much larger doses recommended for epidural anesthesia and have not occurred within the dose range of bupivacaine hydrochloride 0.75% recommended for obstetrical spinal anesthesia. The 0.75% concentration of MARCAINE is therefore not recommended for obstetrical epidural anesthesia. MARCAINE Spinal (bupivacaine HCl 0.75% with dextrose 8.25%) is recommended for spinal anesthesia in obstetrics.

**Nursing Mothers:** It is not known whether local anesthetic drugs are excreted in human milk; therefore, caution should be exercised when local anesthetics are administered to a nursing woman.

**Pediatric Use:** Until further experience is gained in patients younger than 18 years, administration of MARCAINE Spinal in this age group is not recommended.

**ADVERSE REACTIONS:** Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. The most commonly encountered acute adverse experiences following spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or under-ventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site, or from unintentional intravascular injection of a local anesthetic solution. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

**Respiratory System:** Respiratory paralysis or under-ventilation may result from upward extension of the level of spinal anesthesia and may lead to secondary hypoxic cardiac arrest if untreated. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation may contribute to under-ventilation. This will usually occur within minutes of the injection of spinal anesthetic solution, but because of differing maximal onset times, intermittent drug use, and surgical manipulation, it may occur at any time during surgery or the immediate recovery period.

**Cardiovascular System:** Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunken blood and interstitial fluid volumes, cephalad spread of the local anesthetic and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias and possibly cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

**Central Nervous System:** Respiratory paralysis or under-ventilation secondary to cephalad spread of the level of spinal anesthesia (see Respiratory System) and hypotension for the same reason (see Cardiovascular System) are the two most commonly encountered central nervous system-related adverse observations which demand immediate countermeasures.

High doses, or inadvertent intravascular injections may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.

**Neurologic:** Adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and also depend on the particular drug used, the route of administration and the physical status of the patient. Many effects may be related to local anesthetic techniques, with or without a contribution from the drug.

Neurologic effects following spinal anesthesia may include loss of perineal sensation and sexual function, persistent anesthesia, paresthesia, weakness and paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete or no recovery, hypotension, high or total spinal block; urinary retention, headache, backache; septic meningitis; meningismus; arachnoiditis; slowing of labor; increased incidence of forceps delivery; shivering; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid; fecal and urinary incontinence.

**Allergic:** Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions include urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptomatology (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported.

**Other:** Nausea and vomiting may occur during spinal anesthesia.

**OVERDOSAGE:** Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to under-ventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia due to relaxation of sympathetic tone or contributory mechanical obstruction of venous return.

**Management of Local Anesthetic Emergencies:** The first consideration is prevention through careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. Administer oxygen at the first sign of change. The first step in managing systemic toxic reactions, as well as under-ventilation or apnea due to a high or total spinal is to immediately establish and maintain a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. A 50 mg to 100 mg bolus IV injection of succinylcholine will paralyze the patient without depressing central nervous or cardiovascular systems and facilitate ventilation. A bolus IV dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after instituting these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and when appropriate, a vasopressor dictated by the clinical situation. Hypotension may be managed with intravenous fluids, in an attempt to relieve mechanical obstruction of venous return or by using vasopressors and, if indicated, by giving plasma expanders or whole blood.

Endotracheal intubation, employing drugs and techniques familiar to the physician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in maintaining a patent airway or if prolonged ventilatory (assisted or controlled) support is indicated.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Under-ventilation or apnea due to a high or total spinal may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, standard cardiopulmonary resuscitative measures should be instituted and maintained for a prolonged period if necessary. Recovery has been reported after prolonged resuscitative efforts.

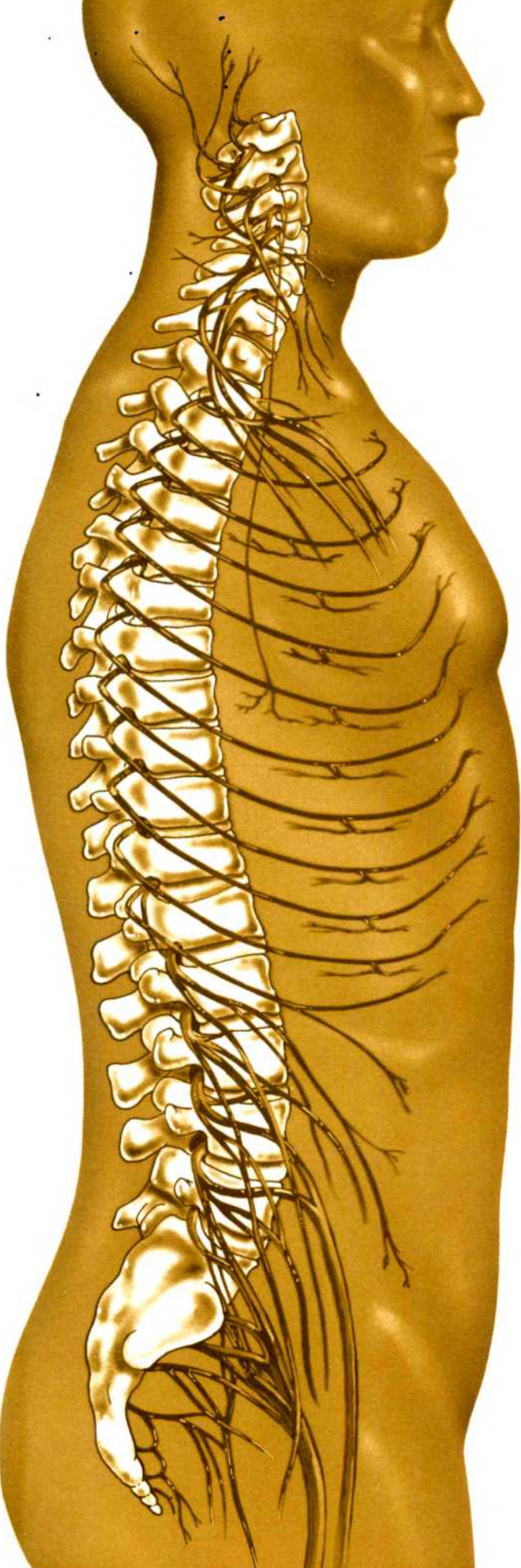
The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous LD<sub>50</sub> in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

**Composition of MARCAINE Spinal Solutions:** Each 1 mL of MARCAINE Spinal contains 7.5 mg bupivacaine hydrochloride and 82.5 mg dextrose. The pH of this solution is adjusted between 4.0 and 6.5 with sodium hydroxide or hydrochloric acid. The specific gravity of MARCAINE Spinal is between 1.030 and 1.035 at 25°C, and 1.03 at 37°C. MARCAINE Spinal does not contain any preservatives.

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Division of Sterling Drug Inc.  
New York, NY 10016



# Introducing a reliable anesthetic for spinal anesthesia

## Few spinal anesthetic failures

New Marcaine® Spinal offers the advantage of dependable and profound anesthesia for a wide variety of surgical and obstetrical procedures. **MARCAINE** Spinal in a dose of 7.5 mg had only one anesthetic failure in 121 patients.\*<sup>1</sup>

## "...reliable local anesthetic solution for spinal anesthesia!"<sup>1</sup>

- ▲ Rapid onset—within one minute
- ▲ Long duration—two to three hours
- ▲ Premixed hyperbaric solution
- ▲ No added bisulfites

## **Marcaine®** *Spinal* (bupivacaine HCl, USP, 0.75% with dextrose, USP, 8.25% injection)

\*in a dose of 7.5 mg for perineal and lower extremity surgery

**Winthrop-Breon**

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Division of Sterling Drug Inc.  
New York, NY 10016

**Reference:**

<sup>1</sup> Moore DC. Spinal anesthesia: Bupivacaine compared with tetracaine. *Anesth Analg* 1980; 59:743-750.

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## Effects of Colloid or Crystalloid Administration on Pulmonary Extravascular Water in the Postoperative Period After Coronary Artery Bypass Grafting

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GALLAGHER JD, MOORE RA, KERNS D, JOSE AB, BOTROS SB, FLICKER S, NAIDECH H, CLARK DL. Effects of colloid or crystalloid administration on pulmonary extravascular water in the postoperative period after coronary artery bypass grafting. *Anesth Analg* 1985;64:753-8.

*The effect of postoperative fluid management on pulmonary extravascular thermal volume (ETV<sub>L</sub>) as an index of pulmonary extravascular water after coronary artery bypass grafting was compared, using the thermal-dye technique, among five patients who received 5% albumin (group A), five patients who received 6% hydroxyethyl starch (group H), and five who received lactated Ringer's solution (group C). Intraoperatively, all patients received lactated Ringer's solution intravenously, and the cardiopulmonary bypass (CPB) circuit prime included 5% albumin. No statistically significant changes in ETV<sub>L</sub> occurred postoperatively in any group, nor did ETV<sub>L</sub> differ significantly between groups. After CPB, colloid osmotic pressure (COP) significantly decreased and pulmonary artery wedge pressure (WP) and the WP-COP gradient significantly increased in each group,*

*implying an increase in transcapillary fluid flux. Cardiac index changed variably. Pulmonary shunt fraction ( $\dot{Q}_{sp}/\dot{Q}_t$ ) did not change in groups A and C but decreased during CPB in group H (from  $0.22 \pm 0.03$  to  $0.16 \pm 0.11$ ). Postoperatively, patients in the three groups received similar volumes of fluids and had similar perioperative weight gains. By the next morning (AM<sub>1</sub>), COP increased in all groups, returning to levels noted before CPB in group C, and exceeding these levels in groups A and H. Wedge pressure was similar in all three groups on AM<sub>1</sub>. PaO<sub>2</sub> decreased significantly, and alveolar-arterial oxygen partial pressure difference increased significantly in all groups on AM<sub>1</sub>. In Group H,  $\dot{Q}_{sp}/\dot{Q}_t$  returned to levels observed before CPB by AM<sub>1</sub> ( $0.27 \pm 0.09$ ). We conclude that in patients without postoperative increases in WP, ETV<sub>L</sub> changes minimally during CPB and is not influenced by the type of fluid administered as the primary volume replacement in the postoperative period.*

**Key Words:** FLUID BALANCE—albumin, crystalloid, hydroxyethyl starch. LUNG—extravascular water. SURGERY—cardiovascular.

Byrick et al. (1) have found that accumulation of pulmonary extravascular water after coronary artery bypass grafting (CABG) is not affected by priming the extracorporeal circuit with colloid or crystalloid solutions. Postoperative fluid management was not discussed, although administration of colloid or crystalloid solutions might have changed pulmonary extravascular water by altering the plasma colloid oncotic pressure, a fundamental determinant of pulmonary transcapillary fluid flux. Accordingly, we

evaluated the effects of postoperative volume replacement with albumin, hydroxyethyl starch, or lactated Ringer's solution on pulmonary extravascular thermal volume (ETV<sub>L</sub>) as an index of pulmonary extravascular water (2) in patients after CABG.

### Methods

The hospital human studies committee approved this study, and informed written consent was obtained from the fifteen patients scheduled for elective myocardial revascularization with aortocoronary saphenous vein grafts. Patients with significant left main coronary artery stenosis, poor left ventricular function (left ventricular end diastolic pressure (LVEDP) greater than 18 mm Hg, or left ventricular ejection fraction (LVEF) less than 50% at catheterization, or both), or

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significant abnormalities in preoperative pulmonary function were excluded. All patients received  $\beta$ -adrenergic antagonists until the morning of surgery and were premedicated with  $0.1 \text{ mg} \cdot \text{kg}^{-1}$  body weight of morphine intravenously and  $0.3\text{--}0.4 \text{ mg}$  of scopolamine intramuscularly, 1 hr before the operation. In the operating room, ECG leads 2 and  $V_5$  were monitored, and a peripheral intravenous cannula was inserted. A 5-Fr double-lumen thermistor-tipped femoral artery catheter (American Edwards Laboratories, Santa Ana, CA) and a quadrilumen thermodilution pulmonary artery catheter were inserted. Anesthesia was induced with  $50 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$  of fentanyl intravenously, and tracheal intubation followed relaxation with  $0.1 \text{ mg} \cdot \text{kg}^{-1}$  of pancuronium intravenously. Patients were ventilated with 100% oxygen, and  $\text{PaCO}_2$  was maintained between 35 and 40 mm Hg during surgery. Before cardiopulmonary bypass (CPB), patients received volumes of lactated Ringer's solution (LR) sufficient to maintain pulmonary artery wedge pressure (WP) between 12 and 14 mm Hg. Right atrial-to-aortic bypass was established using a bubble oxygenator primed with 1000 ml of LR and 1000 ml of 5% albumin. Hypothermic CPB was maintained at a rectal temperature between 26 and  $28^\circ\text{C}$ , a blood flow of  $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{M}^{-2}$ , and a mean arterial pressure between 60 and 90 mm Hg. The left ventricle was vented, and lungs were statically inflated (5 cm  $\text{H}_2\text{O}$  pressure) with oxygen during CPB. After weaning from CPB, sufficient fluids (LR or "pump blood") were given to maintain WP between 12 and 18 mm Hg, depending on the patient's hemodynamic response to volume loading.

Upon arrival at the intensive care unit, patients were divided into three equal groups by a computer-generated randomization scheme. Group C received LR, group H received 6% hydroxyethyl starch, and group A received 5% albumin in quantities sufficient to maintain WP between 12 and 18 mm Hg. Packed red blood cells were given for hemoglobin levels less than  $9 \text{ g} \cdot \text{dl}^{-1}$ , and fresh frozen plasma was given for clotting factor deficiencies.

Plasma colloid osmotic pressure (COP) and WP were measured, as was cardiac index (CI) in duplicate using the thermodilution technique. Arterial and mixed-venous blood samples were obtained while the patient breathed 100% oxygen. Hemoglobin concentration (Hgb) was measured, and alveolar-arterial oxygen partial pressure difference ( $P(A-a)\text{O}_2$ ) and pulmonary shunt fraction ( $\dot{Q}_{\text{sp}}/\dot{Q}_{\text{t}}$ ) were calculated using standard formulas. In each patient,  $\text{ETV}_L$  was determined in duplicate by a lung-water computer (Model 9310, American Edwards Laboratories, Santa Ana, CA) using the thermal dye double-indicator dilution tech-

nique.  $\text{ETV}_L$  measurements were made by methods previously described (2,3), using 10 ml of iced 5% dextrose water containing 5 mg of indocyanine green dye as the diffusible and nondiffusible indicators, respectively.

Thermodilution cardiac output and dye and thermal mean transit times were calculated by the computer.  $\text{ETV}_L$  was calculated as the product of cardiac output and the difference in mean transit times between the thermal and dye markers. Blood was reinfused after each determination.

Three sets of measurements were made, one 15 min after tracheal intubation, but before incision; one after chest closure; and the third in the intensive care unit (ICU) on the morning after surgery ( $\text{AM}_1$ ). Patients were weighed, and total fluids administered during the perioperative period were tabulated. The femoral and pulmonary artery catheters were then removed, and patients were transferred from the ICU.

Statistical analysis was performed using two-factor mixed design analysis of variance for repeated measures (4) followed by a Bonferroni's *t*-test (5) evaluation of significant *F*-ratios. Comparisons of differences in demographic data among groups were made using one-way analysis of variance. Spearman's rank-order correlation and linear regression analysis were performed to evaluate correlations between variables. All results are reported as mean  $\pm$  SEM, and statistical significance is assumed at the  $P < 0.05$  level.

## Results

Patients in group C were older than those in groups H or A ( $P < 0.025$ ) and had better LVEF values at the time of preoperative catheterization ( $P < 0.05$ ). Otherwise, groups were similar with respect to sex, history of prior myocardial infarction, number of bypass grafts placed, and smoking history. One group C patient briefly required administration of a positive inotropic drug after bypass (Table 1).

No significant changes in  $\text{ETV}_L$  were seen in any group, and no differences were noted between groups. In group A, CI decreased significantly ( $P < 0.025$ ) after CPB but returned to pre-CPB levels by  $\text{AM}_1$  (Table 2).

In all groups, COP decreased after CPB ( $P < 0.001$ ). By  $\text{AM}_1$ , COP in group C returned to pre-CPB levels, although in groups A and H, COP levels on  $\text{AM}_1$  were greater than those observed before CPB. On  $\text{AM}_1$ , COP in group H was greater than in groups A and C ( $P < 0.05$ ), and COP in group A was greater than in group C ( $P < 0.05$ ). Wedge pressure increased in all three groups after CPB ( $P < 0.001$ ), but returned toward pre-CPB levels in groups C and H by  $\text{AM}_1$ .



Table 1. Characteristics of Patients Studied

	Experimental group <sup>a</sup>		
	A	C	H
No. of patients	5	5	5
No. of females	0	1	1
Age (yr) <sup>b</sup>	55.8 ± 2.8	65.4 ± 1.6 <sup>d</sup>	52.0 ± 5.3
History of myocardial infarction	1	2	2
History of smoking	4	3	3
Cardiac catheterization			
LVEF (%) <sup>b</sup>	59.2 ± 4.9	67.0 ± 3.7	53.2 ± 3.8
LVEDP <sup>b</sup>	9.4 ± 1.5	8.6 ± 2.1	9.6 ± 3.2
Surgery			
No. of grafts <sup>c</sup>	3.0 ± 0.3	2.8 ± 0.4	2.4 ± 0.2
Postop Inotropes	0	1	0

<sup>a</sup>Experimental groups A, C, and H received 5% albumin (group A), lactated Ringer's solution (group C), or 6% hydroxyethyl starch (group H) for postoperative volume replacement after CABG.

<sup>b</sup>mean ± SEM.

<sup>c</sup> $P < 0.05$  compared to groups A and H.

<sup>d</sup> $P < 0.025$  compared to groups A and H.

There were no significant differences in WP in the three groups in AM<sub>1</sub>. The WP-COP gradient increased in all three groups during surgery ( $P < 0.001$ ), and returned to pre-CPB levels by AM<sub>1</sub> in groups A and C, although the gradient decreased to less than pre-CPB levels ( $-11.4 \pm 1.4$  vs  $-8.4 \pm 1.4$  mm Hg) in group H. On AM<sub>1</sub>, the WP-COP gradient in group H was significantly more negative than in groups A and C ( $P < 0.05$ ).

Hemoglobin concentration decreased in all groups after CPB, significantly in groups A and C, and returned towards pre-CPB levels by AM<sub>1</sub>. There were no significant differences among groups.

PaO<sub>2</sub> decreased significantly and P(A-a)O<sub>2</sub> increased significantly by AM<sub>1</sub> in all groups. Q<sub>sp</sub>/Q<sub>t</sub> did not change in groups A and C. In group H, Q<sub>sp</sub>/Q<sub>t</sub> decreased from  $0.22 \pm 0.03$  to  $0.16 \pm 0.05$  after CPB, but by AM<sub>1</sub> it had increased significantly to  $0.27 \pm 0.04$ .

Table 3 details intraoperative and postoperative fluid management in each group of patients. Intraoperatively, all groups received similar volumes of intravenous solutions, including packed erythrocytes; and similar fluid volumes during CPB, including the circuit prime, cardioplegic solution, and added volume. Total output, including sponge and suction blood loss, and urine, was similar; although no estimate of blood loss to the surgical drapes was made. Each group had a positive fluid balance during surgery.

During the study period in the ICU, similar volumes of intravenous fluids, including blood, were administered to each group. In group A, 47% of fluid administered during the study period was albumin.

In group H, 46% of fluid administered was hydroxyethyl starch, and in group C, all nonblood fluids given were crystalloids. Total output, including urine and chest tube drainage, and net fluid balance were similar in each group. One patient in group A received two units of fresh frozen plasma.

Group A patients gained  $2.42 \pm 1.26$  kg after surgery. Group C patients gained  $1.56 \pm 1.28$  kg and group H patients gained  $1.41 \pm 0.91$  kg. These weight gains were not significantly different. Chest x-rays obtained immediately upon arrival in the ICU and on AM<sub>1</sub> showed no evidence of pulmonary edema or atelectasis in any patient. All patients were extubated after the AM<sub>1</sub> measurements were made. In the ICU, group A patients were studied for  $17.9 \pm 2.49$  hr (mean ± SD), group C patients for  $17.45 \pm 1.89$  hr, and group H patients for  $16.71 \pm 2.28$  hr. These study durations are not significantly different. No correlation was found between change in ETV<sub>L</sub> between measurement points and changes in other measured variables.

## Discussion

Diverse phenomena contribute to increases in pulmonary extravascular water after CABG. A syndrome of severe pulmonary capillary leakage causing interstitial or alveolar pulmonary edema ("pump lung") has been identified (6) but was not observed in our patients. Platelet aggregates, leukocyte breakdown products (7), and complement-mediated leukostasis (8) may alter pulmonary function after bypass. Overdistention and damage of the pulmonary capillaries during CPB also can occur, due to increased blood flow from the bronchial circulation or inadequate venting of the left ventricle. Pulmonary collapse during CPB may aggravate these problems. In our study the left ventricle was vented, and the lungs were statically inflated with oxygen (9). Postoperative left ventricular failure, manifested as low cardiac output and elevated WP, may contribute to postoperative pulmonary dysfunction but was not encountered in our patients.

During CPB with a hypooncotic prime, after an initial decrease in COP, an incomplete compensatory increase in COP takes place due to both an efflux of water from the intravascular to extravascular space and to an influx of albumin from mobilizable peripheral albumin stores (10). The decrease in COP caused by hemodilution increases transcapillary fluid flux through its effect on microvascular oncotic pressure. However, a 50% decrease in COP may be required to produce significant increases in pulmonary extravascular water (11), and such a reduction in COP was

Table 2. Measured Variables<sup>a</sup> in Groups A, C, and H

Measured variable	Group <sup>b</sup>	Before CPB	Measurement period	
			After CPB	AM <sub>1</sub>
ETV <sub>L</sub> (ml·kg <sup>-1</sup> )	A	3.11 ± 0.47	3.35 ± 0.47	2.86 ± 0.22
	C	3.43 ± 0.33	4.04 ± 0.47	2.76 ± 0.41
	H	2.95 ± 0.46	3.52 ± 0.26	2.99 ± 0.25
CI (L·min <sup>-1</sup> ·M <sup>-2</sup> )	A	2.75 ± 0.21	2.11 ± 0.46 <sup>d</sup>	2.96 ± 0.25
	C	2.50 ± 0.17	2.74 ± 0.38	3.07 ± 0.37
	H	2.47 ± 0.20	2.30 ± 0.13	2.70 ± 0.21
COP (mm Hg)	A	18.1 ± 0.8	15.9 ± 0.4 <sup>c</sup>	20.7 ± 1.1 <sup>c,x</sup>
	C	16.2 ± 0.9	14.5 ± 0.6 <sup>c</sup>	17.1 ± 0.8
	H	19.4 ± 1.0	15.2 ± 1.1 <sup>c</sup>	23.9 ± 0.9 <sup>c,d</sup>
WP (mm Hg)	A	10.6 ± 1.7	13.6 ± 2.0 <sup>c</sup>	13.6 ± 0.9 <sup>c</sup>
	C	11.8 ± 3.2	15.4 ± 1.1 <sup>c</sup>	13.2 ± 1.2
	H	10.6 ± 0.9	16.6 ± 1.4 <sup>c</sup>	13.8 ± 1.2
WP-COP (mm Hg)	A	-7.5 ± 1.3	-2.1 ± 2.0 <sup>c</sup>	-7.1 ± 1.3
	C	-3.5 ± 3.0	1.8 ± 0.8 <sup>c</sup>	-4.6 ± 1.4
	H	-8.4 ± 1.4	1.9 ± 1.8 <sup>c</sup>	-11.4 ± 1.4 <sup>c</sup>
Hgb (g·dl <sup>-1</sup> )	A	12.2 ± 0.3	9.3 ± 0.3 <sup>c</sup>	10.9 ± 0.8
	C	11.5 ± 0.4	8.5 ± 0.4 <sup>c</sup>	10.9 ± 0.5 <sup>b</sup>
	H	11.3 ± 0.9	9.0 ± 0.6	10.9 ± 0.5
PaO <sub>2</sub> (mm Hg)	A	4.43 ± 11.7	487.3 ± 46.0	221.9 ± 43.0 <sup>c</sup>
	C	499.8 ± 27.3	393.4 ± 63.7	257.9 ± 62.1 <sup>c</sup>
	H	482.8 ± 24.3	487.5 ± 56.8	194.5 ± 48.3 <sup>c</sup>
P(A-a)O <sub>2</sub> (mm Hg)	A	255.7 ± 33.6	193.0 ± 46.6	457.8 ± 43.8 <sup>c</sup>
	C	174.9 ± 27.1	285.4 ± 63.1	415.1 ± 62.4 <sup>c</sup>
	H	203.9 ± 29.0	198.1 ± 57.0	477.6 ± 48.9 <sup>c</sup>
Q <sub>sp</sub> /Q <sub>t</sub>	A	0.26 ± 0.02	0.19 ± 0.05	0.27 ± 0.04
	C	0.22 ± 0.03	0.24 ± 0.05	0.28 ± 0.04
	H	0.22 ± 0.03	0.16 ± 0.05	0.27 ± 0.04 <sup>b</sup>

<sup>a</sup>mean ± SEM.<sup>b</sup>As defined in text and Table 1.<sup>c</sup>P < 0.05 compared to before CPB measurement.<sup>d</sup>P < 0.025 compared to before CPB measurement.<sup>e</sup>P < 0.001 compared to before CPB measurement.<sup>f</sup>P < 0.05 compared to groups A and C.<sup>g</sup>P < 0.05 compared to group C.<sup>h</sup>P < 0.05 compared to after CPB measurement.

not observed in our patients. The ability of the lymphatics to remove pulmonary interstitial fluid, normally an important protective mechanism countering potential increases in pulmonary extravascular water (12), has not been evaluated immediately after CPB.

In the study of Byrick et al. (1), in 17 patients undergoing CABG, pulmonary extravascular water increased, though not significantly, after CPB. They found that pulmonary extravascular water continued to increase on the first and second postoperative days and that the WP-COP gradient correlated with the increase on the first postoperative day. Intraoperative use of colloid neither influenced postoperative pulmonary extravascular water accumulation in the study of Byrick et al. (1), nor altered perioperative fluid requirements in a study performed by Hallowell et al. (13). We questioned whether postoperative colloid administration, by restoring COP levels to or above normal, would prevent the continued accumulation

of pulmonary extravascular water and reduce postoperative fluid requirements. Hydroxyethyl starch, a colloid substitute less expensive than albumin, has been used successfully as a pump priming solution for CPB (14), and was evaluated as an alternative to albumin.

The decrease in ETV<sub>L</sub> in our patients on AM<sub>1</sub> contrasts with the continued increase in ETV<sub>L</sub> noted by Byrick et al. (1). Changes in COP observed by Byrick et al. (1), from 18.9 ± 0.7 mm Hg before the incision was made to 14.2 ± 0.8 mm Hg after CPB, were similar to those of our group C (16.2 ± 0.9 to 14.5 ± 0.6 mm Hg). However, by AM<sub>1</sub>, COP in our group C patients was 17.1 ± 0.8 mm Hg, while in the study of Byrick et al. (1), COP remained decreased at 13.9 ± 0.7 mm Hg. Because Byrick et al. (1) do not detail their postoperative management, we cannot determine the cause of the difference between our observations but suggest that the persistently decreased

Table 3. Perioperative Fluid Management<sup>a</sup>

Intraoperative						
Group <sup>b</sup>	Intravenous fluids		Cardiopulmonary bypass (includes prime and added volume)	Output		Fluid balance
	Total (includes blood)	Blood		Total <sup>c</sup>	Urine	
A	3600 ± 374.5	454 ± 91.3	4355 ± 459.8	2343 ± 214.1	981 ± 164.1	+5612 ± 463.5
C	3816 ± 365.9	295 ± 108.3	3900 ± 480.0	2367 ± 241.3	984 ± 327.3	+5349 ± 317.9
H	3288 ± 561.1	300 ± 122.3	3970 ± 361.9	2069 ± 183.7	893 ± 177.9	+5189 ± 779.5
Postoperative						
Group	Intravenous fluids		% of fluids made up by test solution	Output		Fluid balance
	Total	Blood		Total	Chest tube drainage	
A	3313 ± 401.4	560 ± 149.2	47%	3547.2 ± 483.2	517.8 ± 34.2	-223.4 ± 453.5
C	3109.6 ± 329.2	588.0 ± 112.5	81%	2923.8 ± 178.3	689.4 ± 51.8	+185.8 ± 434.3
H	3707.6 ± 390.2	556 ± 72.6	46%	3569 ± 427.8	593 ± 125.1	+138.6 ± 490.9

<sup>a</sup>ml; mean ± SEM.<sup>b</sup>Groups defined in text and Table 1.<sup>c</sup>Includes suction and sponge blood loss and urine output; no estimate of blood loss to surgical drapes made.

COP in their patients (1) produced the ETV<sub>L</sub> accumulation noted.

Sivak et al. (3) studied nine patients using the thermal dye technique. They found no change in ETV<sub>L</sub> after CPB, but a significant decrease was observed the next morning. Our failure to find a decrease in ETV<sub>L</sub> on AM<sub>1</sub> may be related to the oxygenator used. We used bubble oxygenators, which have been shown to increase postoperative ETV<sub>L</sub> (15), although Sivak et al. (3) used a membrane oxygenator, which does not increase ETV<sub>L</sub> (15).

Certain aspects of our study require comment. Patients in group C were older but had better LVEF than groups A or H. We have shown that age is not a major determinant of pulmonary extravascular water accumulation during CABG (16), and in the present study LVEF was normal in all groups. When blood is not used in the pump prime, the average patient gains between 1.8 and 2.7 kg (17). Mean weight gain in our patients, 1.63 kg, falls within this range and did not differ significantly among the three groups.

During aortic reconstructive surgery, Virgilio et al. (18) found that twice the volume of crystalloid as of colloid was required for hemodynamic resuscitation, and that crystalloid administration resulted in a positive fluid balance of 8.4 ± 0.8 liters, vs a 3.4 ± 0.4 liter positive fluid balance when 5% albumin was given. However, in a study analogous to the current investigation, Boutros et al. (19) compared effects of colloid and crystalloid administered after abdominal surgery to patients who received LR intraoperatively. Colloid and crystalloid groups received 3.5–4 liters of LR intraoperatively. Postoperatively, WP was maintained

within 2 mm Hg of preoperative values. During the first 24 hr, colloid and crystalloid groups received similar fluid volumes (2 L·M<sup>-2</sup>) and produced similar volumes of urine (1 L·M<sup>-2</sup>), despite 20% increases in serum albumin in the colloid group and decreases in serum albumin in the crystalloid groups. In the study of Boutros et al. (19) and in the present study, the volume of colloid administered postoperatively, as a fraction of the total volume administered in the perioperative period, may have been insufficient to influence volume requirements between the LR and colloid group.

In patients undergoing CABG with normal preoperative left ventricular function, ETV<sub>L</sub> did not significantly change during CPB with the bubble oxygenator used in this study. Postoperative administration of 5% albumin, 6% hydroxyethyl starch, or LR as the primary volume replacement fluid did not affect ETV<sub>L</sub>. Postoperative myocardial or pulmonary dysfunction was not seen in our patients, so we cannot comment on the possible role of postoperative fluid therapy in the genesis of such dysfunctions.

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## Regional Blood Flows during Induced Hypotension Produced by Nitroprusside or Trimethaphan in the Rhesus Monkey

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SIVARAJAN M, AMORY DW, MCKENZIE SM. Regional blood flows during induced hypotension produced by nitroprusside or trimethaphan in the rhesus monkey. *Anesth Analg* 1985;64:759-66.

*In monkeys anesthetized with 70% nitrous oxide and 0.5% inspired halothane in oxygen, we measured changes in systemic hemodynamics and regional blood flows produced by nitroprusside and trimethaphan. Regional blood flow measurements were made using the radioactive microsphere technique. Control measurements were made before infusion of nitroprusside and trimethaphan into each animal in sequence in amounts adequate to reduce mean arterial pressure to approximately  $55 \pm 5$  mm Hg. Measurements were made during each drug infusion after a stable period of hypotension lasting at least 30 min. During nitroprusside infusion, cerebral blood flow remained unchanged, but myocardial blood flow increased significantly. However, pressure-rate*

*product, an indirect measure of myocardial oxygen consumption, was unchanged, implying that myocardial blood flow exceeded myocardial oxygen requirement. During trimethaphan infusion, cerebral blood flow decreased, although cerebral metabolic rate for oxygen was unchanged due to increased oxygen extraction by the brain. Trimethaphan also produced a decrease in myocardial blood flow that was in proportion to the decrease in myocardial oxygen requirement as indicated by pressure-rate product. Neither drug produced changes in renal or total hepatic blood flows. We conclude that brain oxygen reserve is decreased during hypotension induced by trimethaphan. Blood flows to other organs are not significantly impaired in monkeys during hypotension to a mean arterial pressure of approximately 55 mm Hg induced by either nitroprusside or trimethaphan.*

**Key Words:** ANESTHETIC TECHNIQUES, HYPOTENSIVE—nitroprusside, trimethaphan.

Nitroprusside and trimethaphan are commonly used to produce deliberate hypotension during anesthesia to minimize intraoperative blood loss and to improve operative conditions by decreasing bleeding in the surgical field. Nitroprusside reduces blood pressure by acting directly on blood vessels to produce vasodilation in both the arterial and venous circulations. Trimethaphan is a ganglionic blocking agent that reduces blood pressure mainly by blocking sympathetic activity and reflexes. Because these drugs have different modes of action, their expected effects on regional blood flows may differ also. Isolated measurements of blood flows to different organs during infusion of these drugs have been reported but not simultaneous measurements of regional blood flows. The purpose of this study was to measure regional blood flows simultaneously during hypotension produced by these drugs.

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### Methods

The study was carried out in five rhesus monkeys (*Macaca mulatta*) weighing 5.6–7.1 kg. Anesthesia was induced using ketamine ( $8\text{--}10 \text{ mg}\cdot\text{kg}^{-1}$ ) intramuscularly, and the trachea was then intubated after pancuronium ( $0.1 \text{ mg}\cdot\text{kg}^{-1}$ ) was given intravenously. Anesthesia was maintained using 70% nitrous oxide and 0.5% inspired halothane in oxygen. The animals were mechanically ventilated at a tidal volume of  $10 \text{ ml}\cdot\text{kg}^{-1}$  and a rate sufficient to maintain  $\text{PaCO}_2$  at approximately 40 mm Hg. A catheter was inserted into the left atrium through a thoracotomy in the left fourth intercostal space, which was then closed after aspiration of air in the pleural space. Catheters were also inserted into the abdominal aorta and inferior vena cava via the left femoral vessels, and into the jugular bulb via the right internal jugular vein. Body temperature was maintained at  $37^\circ\text{C}$  (rectal) using a heating pad. Lactated Ringer's solution was continuously infused at the rate of  $2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ , and blood loss was replaced with three times the volume of lactated Ringer's solution.

Arterial and left atrial pressures were recorded continuously, and mean pressures were derived by elec-

tronic filtering. Control measurements were made approximately 90–120 min after induction of anesthesia. Duplicate measurements of cardiac output ( $\dot{Q}_t$ ) were obtained each time using dye-dilution technique (indocyanine green). Immediately after  $\dot{Q}_t$  determinations, ultrasonically dispersed suspensions of radioactive microspheres were injected into the left atrium for measurement of regional blood flows (see below). Arterial- and jugular-bulb blood samples were analyzed for pH,  $\text{PCO}_2$ ,  $\text{PO}_2$ , oxygen saturation, and hemoglobin content. Arteriovenous oxygen-content difference across the brain was calculated using the standard formula for determination of oxygen content of blood (1).

The experiment was designed so that each animal received both nitroprusside (0.02%) and trimethaphan (0.5%) in sequence with time for recovery between drug infusions. Preliminary studies had shown that monkeys become resistant to both nitroprusside and trimethaphan and that high infusion rates of both drugs are necessary to maintain blood pressure at hypotensive levels. However, recovery of blood pressure to control levels is prolonged (usually longer than 2 hr) after discontinuation of trimethaphan infusion, but not after discontinuation of nitroprusside infusion. In order to avoid the hemodynamic effects of prolonged halothane anesthesia (2), we decided to infuse nitroprusside first in all animals. After control measurements, nitroprusside was infused using a variable-speed Harvard infusion pump. Mean arterial pressure was lowered to approximately 55 mm Hg and was maintained at this level by continuous infusion of the drug for at least 30 min before  $\dot{Q}_t$  and regional blood flow measurements were repeated. Infusion of nitroprusside was then stopped, and the animals were allowed to recover for at least an hour after restoration of mean arterial pressure to control levels before another set of control measurements was made. Infusion of trimethaphan was then begun, and measurements were repeated after maintaining a similar level of hypotension by continuous infusion of the drug for at least 30 min.

Regional blood flow determinations were made by the radioactive microsphere technique described previously (3). Briefly, for each determination, a suspension of microspheres 50  $\mu\text{m}$  in diameter labeled with one of five  $\gamma$ -emitting nuclides ( $^{46}\text{scandium}$ ,  $^{95}\text{niobium}$ ,  $^{85}\text{strontium}$ ,  $^{51}\text{chromium}$ , and  $^{141}\text{cerium}$ ) was injected into the left atrium. The microspheres were distributed to each organ in proportion to its blood flow and trapped in organ arterioles. At the end of the experiment, the animal was exsanguinated, and all organs and representative aliquots of bone, muscle, and skin were counted for radioactivity. A composite emission

spectrum from each organ or tissue representing four isotopes was processed by a PDP-15 digital computer to correct for overlapping spectra and thus derive radioactive counts of each isotope. Blood flows ( $\text{ml}\cdot 100\text{ g of tissue}^{-1}\cdot\text{min}^{-1}$ ) were calculated from these radioactive counts for each organ and tissue. Total blood flow to the liver was calculated as the sum of hepatic artery flow and portal vein flow. Portal vein flow was calculated as the sum of arterial flows to the gastrointestinal tract, pancreas, and spleen because the microspheres do not enter the portal venous circulation. Blood flow to carcass was derived from radioactivity measured in aliquots of bone and muscle.

The changes in systemic hemodynamic and regional blood flow values during each drug infusion were compared to its preceding control values by use of the Student's *t*-test for paired observations. Control values obtained before each drug infusion were compared to each other, also by the Student's paired *t*-test. To detect differences between the effects of the two drugs, the Student's paired *t*-test was used to compare the differences between control values and values produced by nitroprusside to the differences between control values and values produced by trimethaphan. Changes were considered statistically significant at  $P < 0.05$ .

## Results

Mean total dose of nitroprusside was  $1.05 \pm 0.3\text{ mg}\cdot\text{kg}^{-1}$ . Two of the animals received total doses of nitroprusside exceeding  $1\text{ mg}\cdot\text{kg}^{-1}$  ( $2.1\text{ mg}\cdot\text{kg}^{-1}$  and  $1.2\text{ mg}\cdot\text{kg}^{-1}$ , respectively) but showed no signs of cyanide toxicity as indicated by normal  $\text{pH}_a$ , unchanged cerebral venous oxygen content, and prompt recovery of mean arterial pressure on termination of nitroprusside infusion. Mean total dose of trimethaphan was  $28.0 \pm 10.0\text{ mg}\cdot\text{kg}^{-1}$ . Mean duration of hypotension before measurements of regional blood flows was  $56 \pm 5\text{ min}$  with nitroprusside infusion, and  $41 \pm 3\text{ min}$  with trimethaphan infusion, a difference that was not statistically significant.

Systemic hemodynamic values, cerebral arteriovenous oxygen content differences, and arterial blood-gas tensions are shown in Table 1. Control values before nitroprusside infusion were not significantly different from control values before trimethaphan infusion. Infusion of nitroprusside resulted in significant (32%) increases in heart rate so that during hypotension, with a 37% reduction in mean arterial pressure, pressure-rate product showed only non-significant changes. Cardiac output remained unchanged, but systemic vascular resistance decreased significantly during nitroprusside infusion. During

Table 1. Systemic Hemodynamic Values and Blood-Gas Tensions during Nitroprusside and Trimethaphan Infusion

	Control	Nitroprusside	Control	Trimethaphan	Significance of differences between nitroprusside and trimethaphan
Heart rate (beats·min <sup>-1</sup> )	142 ± 5	188 ± 9 <sup>b</sup>	148 ± 2	147 ± 9	<i>P</i> < 0.01
Mean arterial pressure (mm Hg)	87 ± 5	55 ± 2 <sup>b</sup>	92 ± 4	54 ± 5 <sup>b</sup>	NS
Pressure-rate product × 10 <sup>-2</sup>	162 ± 13	141 ± 11	175 ± 10	107 ± 6 <sup>b</sup>	<i>P</i> < 0.01
Cardiac output (l·min <sup>-1</sup> )	1.09 ± 0.08	1.33 ± 0.09	0.97 ± 0.09	0.96 ± 0.1	NS
Total peripheral resistance (mm Hg·l <sup>-1</sup> ·min)	82 ± 8	43 ± 4 <sup>a</sup>	101 ± 15	63 ± 15 <sup>b</sup>	NS
Cerebral arteriovenous oxygen content difference (ml O <sub>2</sub> ·dl <sup>-1</sup> )	3.1 ± 0.4	3.1 ± 0.6	3.1 ± 1.0	4.2 ± 1.2 <sup>a</sup>	NS
PaO <sub>2</sub>	104 ± 8	93 ± 5	108 ± 7	106 ± 4	NS
Paco <sub>2</sub>	43 ± 2	44 ± 3	43 ± 1	41 ± 3	NS
pH <sub>a</sub>	7.37 ± 0.01	7.36 ± 0.01	7.37 ± 0.01	7.39 ± 0.02	NS

Values represent the mean ± SEM of five animals.

<sup>a</sup>*P* < 0.05, <sup>b</sup>*P* < 0.01; when compared to control values obtained before drug infusion.

NS, nonsignificant.

trimethaphan infusion, heart rate remained unchanged and pressure-rate product decreased significantly (39%). Cardiac output was also unchanged, and systemic vascular resistance decreased significantly during trimethaphan infusion. There was also a significant 35% increase in cerebral arteriovenous oxygen content difference during trimethaphan infusion. Effects of nitroprusside on heart rate and pressure-rate product were significantly different when compared to those during trimethaphan infusion.

Regional blood flow values are shown in Table 2. Again, there were no significant differences between the control values before nitroprusside infusion and those before trimethaphan infusion. Infusion of nitroprusside produced a significant increase (97%) in myocardial blood flow. Blood flows to brain, kidneys, liver, skin, and carcass showed only nonsignificant changes during nitroprusside infusion. During trimethaphan infusion, both myocardial and cerebral blood flows were significantly decreased by 30%. Regional blood flows within the brain (to cerebral hemispheres and cerebellum) were similarly decreased during trimethaphan infusion. There were no other significant changes in regional blood flow during trimethaphan infusion. The increase in myocardial blood flow produced by nitroprusside was significantly different when compared to the decrease produced by trimethaphan. The changes in cerebral blood flow produced by the two drugs were not significantly different. Though neither drug produced a significant change from the control in hepatic blood flow, the compared effects of the two drugs were statistically significant.

Cerebral metabolic rate for oxygen, calculated as

the product of cerebral blood flow and brain arteriovenous oxygen content difference, showed no significant changes during nitroprusside infusion. As a result of increased oxygen extraction by the brain (Fig. 1), cerebral metabolic rate for oxygen during trimethaphan infusion also was unchanged.

## Discussion

Most of the previous studies on regional blood flows during nitroprusside- and trimethaphan-induced hypotension have been in dogs, so that comparison with our study is difficult. Our intent was to alternate the sequence of drug infusion in successive animals; but, due to the prolonged effect of trimethaphan we observed in our preliminary studies, we chose to infuse nitroprusside first in all animals. Complete recovery after termination of nitroprusside infusion was seen in all animals, so that control hemodynamic and regional blood flow values obtained before trimethaphan infusion were similar and not significantly different from control values obtained before nitroprusside infusion. Therefore, we believe that the changes seen during trimethaphan infusion were due to that drug alone. However, we cannot rule out residual effects of nitroprusside modifying the actions of trimethaphan. Although two of the animals received nitroprusside in excess of 1 mg·kg<sup>-1</sup>, they showed no signs of cyanide toxicity as indicated by normal pH<sub>a</sub>, unchanged cerebral venous oxygen content, and prompt recovery of systemic hemodynamic and regional blood flow values to control levels.

The effects of nitroprusside and trimethaphan on our observed systemic hemodynamic values were

Table 2. Regional Blood Flow Changes during Nitroprusside and Trimethaphan Infusion

	Control	Nitroprusside	Control	Trimethaphan	Significance of differences between nitroprusside and trimethaphan
Heart	145 ± 10	287 ± 18 <sup>a</sup>	150 ± 13	105 ± 13 <sup>a</sup>	$P < 0.001$
Brain (total)	112 ± 11	88 ± 12	105 ± 17	74 ± 9 <sup>a</sup>	NS
cerebral hemispheres	114 ± 11	87 ± 12	105 ± 17	73 ± 9 <sup>a</sup>	NS
cerebellum	98 ± 17	88 ± 17	110 ± 21	79 ± 13 <sup>a</sup>	NS
midbrain and brainstem	114 ± 13	99 ± 10	108 ± 20	80 ± 12	NS
Kidneys	810 ± 95	776 ± 75	745 ± 106	832 ± 120	NS
Liver (total) <sup>c</sup>	63 ± 7	71 ± 11	61 ± 7	52 ± 8	$P < 0.05$
Carcass <sup>d</sup>	7 ± 1	13 ± 2	7 ± 1	7 ± 1	NS
Skin	13 ± 4	10 ± 2	12 ± 3	17 ± 4	NS

Regional blood flow values are expressed in ml·100 g of tissue<sup>-1</sup>·min<sup>-1</sup> and represent the mean ± SEM of five animals.

<sup>a</sup> $P < 0.05$ , <sup>b</sup> $P < 0.01$ ; when compared to control values obtained before drug infusion.

<sup>c</sup>Total blood flow to the liver represents sum of hepatic artery and portal vein flows. Portal vein flow is the sum of arterial flows to the gastrointestinal tract, pancreas and spleen.

<sup>d</sup>Carcass consists predominantly of muscles and bones.

NS, nonsignificant.

similar to findings also reported in humans during nitrous oxide and halothane (4-6). During hypotension produced by nitroprusside, reflex increases in heart rate and, as a result, increases in  $\dot{Q}_t$  usually are observed (4,5). Ganglionic blocking effect of trimethaphan may prevent reflex tachycardia and increases in  $\dot{Q}_t$  (6), or may even produce bradycardia and decreases in  $\dot{Q}_t$  (5). Total peripheral resistance is usually decreased during infusions of both drugs (4-6). Such consistent hemodynamic changes have not been observed in dogs, perhaps due to differences in anesthetic technique. Using morphine, pentobarbital, and urethane in dogs, Rowe et al. observed increases in heart rate and no changes in  $\dot{Q}_t$  during trimethaphan infusion (7). Wang et al. used pentobarbital and chloralose and reported no changes in heart rate during nitroprusside infusion. However, they observed significant bradycardia during trimethaphan infusion and significant decreases in  $\dot{Q}_t$  when both drugs were infused (8). Using pentobarbital and pancuronium, Fan et al. reported no changes in heart rate during nitroprusside infusion but variable changes in  $\dot{Q}_t$  (9). Sensitive dogs, which required only small doses of nitroprusside to produce hypotension, had decreases in  $\dot{Q}_t$ ; and "resistant" dogs, which required large doses of nitroprusside, had increases in  $\dot{Q}_t$  (9). These disparate reports strengthen our view that our findings during nitrous oxide-halothane anesthesia are more relevant to clinical practice than findings in dogs during intravenous, usually pentobarbital, anesthesia.

We measured regional blood flows after maintaining hypotension (approximately 55 mm Hg) for a mean duration of  $55 \pm 5$  min and  $41 \pm 3$  min with nitroprusside and trimethaphan, respectively. This duration is sufficient to bring about autoregulation of blood

flow in the various vascular beds (10), so that our regional blood flow measurements reflect steady-state conditions.

Control measurements of cerebral blood flow in our study were high, but similar values have been measured in rhesus monkeys using the radioactive microsphere method (11,12). Use of ketamine and halothane could also account for some of the increase in cerebral blood flow. Fitch et al. reported that in baboons both nitroprusside and trimethaphan produced no changes in cerebral blood flow during halothane anesthesia (13); whereas Michenfelder et al. found that in dogs both nitroprusside and trimethaphan significantly decreased cerebral blood flow (14). Stoyka et al., studying dogs (15), and Maekawa et al., studying cats (16), observed no changes in cerebral blood flow during nitroprusside infusion; but both groups found significant reductions during trimethaphan infusion, findings that are similar to ours. However, Brown et al. reported opposite findings in rhesus monkeys that were anesthetized by phencyclidine (17). Mild reduction (10%) in mean arterial pressure produced by nitroprusside resulted in significant cerebral blood flow decreases in these animals, whereas trimethaphan did not have the same effect (17). The duration of stable hypotension before cerebral blood flow measurements were made was not mentioned in their report (17). It is possible that their blood flow measurements represented a transient response and ours a steady-state response. Though we observed a significant decrease (30%) in cerebral blood flow during trimethaphan infusion, absolute values were above levels generally associated with ischemia (18). Also, in our study the decrease in cerebral blood flow during trimethaphan infusion was accompanied by cor-



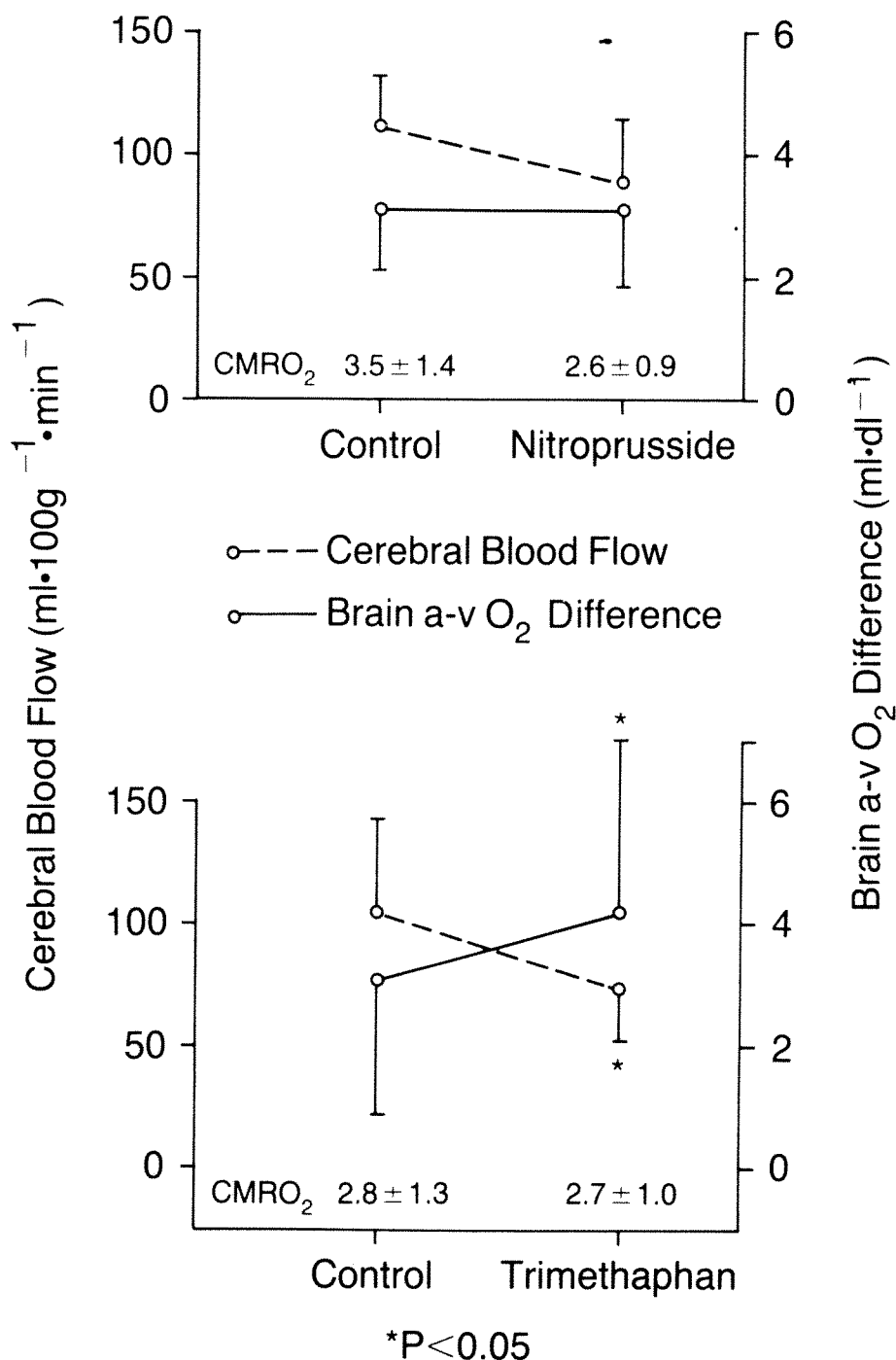


Figure 1. Changes in cerebral blood flows and brain arteriovenous oxygen content differences due to hypotension induced using nitroprusside and trimethaphan. Cerebral metabolic rate for oxygen (CMRO<sub>2</sub>) is expressed in mls of O<sub>2</sub>·100 g of tissue<sup>-1</sup>·min<sup>-1</sup>, and represents mean value ± SD. Vertical bars also represent SD.

responding increases in oxygen extraction by the brain, as evidenced by significant increases in brain arteriovenous oxygen content difference, so that cerebral metabolic rate for oxygen remained constant (Fig. 1). However, if arterial oxygen content had also decreased during trimethaphan infusion, as is likely to occur due to depression of  $\dot{Q}_t$  and hypoxic pulmonary vasoconstriction (19), cerebral ischemia could have occurred. Michenfelder et al. (14) and Maekawa et al.

(16) concluded that brain oxygen availability was significantly less during trimethaphan infusion than during nitroprusside infusion. Our study also suggests that the brain oxygen reserve may be decreased during trimethaphan infusion.

Under normal conditions, myocardial oxygen supply, i.e., blood flow, parallels myocardial oxygen consumption (20). During nitroprusside infusion, we observed a marked increase in myocardial blood flow

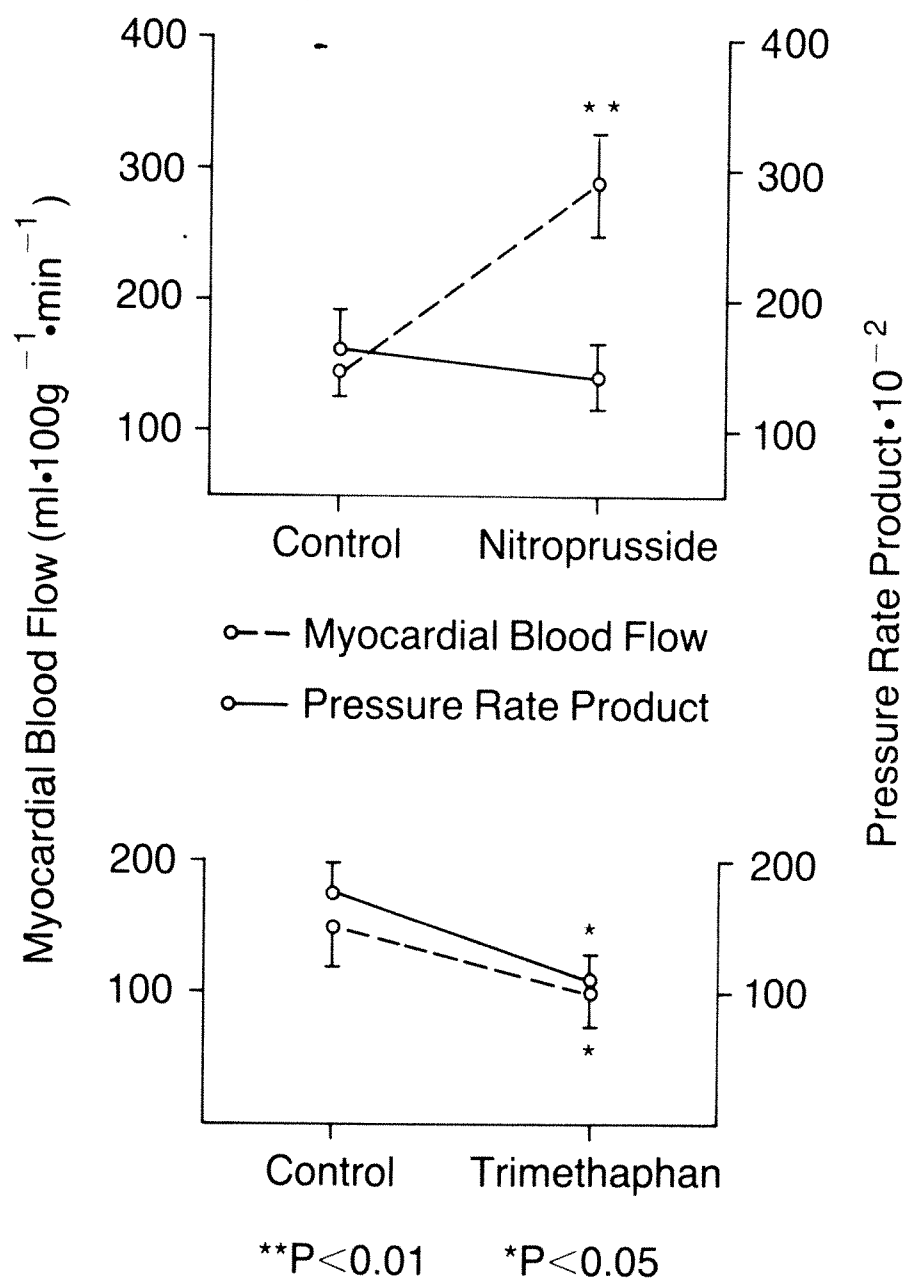


Figure 2. Changes in myocardial blood flows and pressure-rate products due to hypotension induced using nitroprusside and trimethaphan infusion. Vertical bars represent SD.

while pressure-rate product, an indirect index of myocardial oxygen consumption (21), remained unchanged (Fig. 2). This powerful vasodilatory effect of nitroprusside, which implies that the oxygen supply to the myocardium exceeded oxygen needs, also has been observed in dogs (22,23). During trimethaphan infusion we observed parallel decreases in myocardial blood flow and pressure-rate product, suggesting that myocardial oxygenation was not impaired (Fig. 2). Rowe et al. observed somewhat opposite findings in dogs (7). Myocardial blood flow decreased in their experiments, but directly measured myocardial oxygen consumption was unchanged, a result of in-

creased arterial-coronary sinus oxygen content difference. They suggested that myocardial oxygen reserve was decreased (7). We did not measure myocardial oxygen consumption. Further studies are needed, either in humans or other primates, to clarify this issue.

In our experiments, neither drug had any effect on renal blood flow. During nitroprusside infusion in dogs, some investigators have reported increases in renal blood flow (24), some have observed maintenance of renal blood flow (8,25), and some have reported decreases in renal blood flows (26,27). In a study using the radioactive microsphere method to

compare the early effects of nitroprusside and nitroglycerin on regional blood flow in dogs, we also observed that nitroprusside produced an immediate, significant reduction in renal blood flow (28). In patients undergoing nephrolithotomy in the lateral decubitus, Birch and Boyce observed decreases in renal blood flow after nitroprusside administration (29), but one has to question whether autoregulation was present in these patients when their kidneys and renal vessels were being manipulated surgically. Behnia and his colleagues measured creatinine clearance and urine oxygen tension in patients undergoing neurosurgical operations (30). Though creatinine clearance was decreased during nitroprusside-induced hypotension, urine oxygen tension was unchanged. Thus they concluded that renal medullary oxygenation, and hence blood flow, was adequate (30). Disparate effects on renal blood flow also have been observed in dogs during trimethaphan infusion. Wada et al. observed no changes in dog renal medullary blood flow during trimethaphan infusion (31). Wang et al. reported significant decreases in dog renal artery flow during trimethaphan infusion (8). Our findings in monkeys, and the findings of Behnia et al. in human patients (30), suggest that neither nitroprusside nor trimethaphan causes significant impairment of renal blood flow and oxygenation.

We observed no changes in total blood flow to the liver (sum of hepatic artery and portal vein flows) during infusions of either nitroprusside or trimethaphan. Again, this is at variance with findings obtained in dogs during pentobarbital anesthesia. Wang et al. (8) and Gelman et al. (32) reported significant decreases in mesenteric and hepatic blood flow, respectively, during nitroprusside infusion; although Fan et al. reported a decrease in blood flow to the liver during nitroprusside infusion only in dogs that were "resistant" to the drug (9). Trimethaphan also has been reported to decrease hepatic blood flow in dogs (31,33). These findings could be attributed to pentobarbital anesthesia, which may not provide sufficient analgesia to prevent sympathetic response to surgical stimulation. Because the splanchnic vascular bed has rich sympathetic innervation, sympathetic stimulation causes an immediate decrease in splanchnic blood flow (34). We administered nitrous oxide and halothane, a potent inhalation anesthetic; hence, sympathetic tone in our animals was probably only slightly elevated, if at all. Under such conditions we observed no changes in hepatic blood flow. Autoregulation of hepatic and splanchnic arterial blood flows has been demonstrated under some conditions, but autoregulation of portal vasculature does not occur (10,35). Portal vein flow is principally determined by

vascular resistance of the intestines (35). Portal vein flow in our study was calculated as the sum of splanchnic arterial flows. It is possible that halothane reduced sympathetic tone in our animals, resulting in splanchnic vasodilation and decreases in splanchnic vascular resistance, thus maintaining portal vein flow and total hepatic blood flow. In support of this hypothesis is the study of dogs by Colley et al., in which they reported that hypotension induced by nitroprusside during halothane anesthesia also produced no changes in hepatic blood flow (28). In patients anesthetized with halothane, Salam et al. measured clearance of indocyanine green as an index of hepatic function during nitroprusside-induced hypotension (36). They reported no changes in hepatic function. Our study in monkeys, the study by Colley et al. in dogs (28), and the clinical study reported by Salam et al. (36) indicate that hepatic blood flow and function are not significantly impaired by hypotension induced with nitroprusside or trimethaphan during halothane anesthesia.

In this study designed to simulate clinical anesthesia by the use of nitrous oxide and halothane in oxygen, we found that nitroprusside significantly increased myocardial blood flow in excess of apparent myocardial oxygen demand. Trimethaphan significantly decreased cerebral blood flow, but cerebral metabolic rate for oxygen remained unchanged. Trimethaphan also decreased myocardial blood flow, but this reduction was proportional to reduction in apparent myocardial oxygen demand. Neither drug had any effect on renal or total hepatic blood flow.

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## Decreased Sensitivity to Metocurine in Patients with Upper Motoneuron Disease

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SHAYEVITZ JR, MATTEO RS. Decreased sensitivity to metocurine in patients with upper motoneuron disease. *Anesth Analg* 1985;64:767-772.

*Responses to the nondepolarizing muscle relaxant, metocurine, were studied in eight hemiplegic and eight unmatched patients with normal motor strength during the general anesthetic given for various neurosurgical operations. Metocurine, 0.3 mg/kg, was administered intravenously, and indirectly evoked thumb twitch tensions were measured on both sides in the hemiplegic patients, and on one side in the normal patients. Arterial blood samples were obtained as twitch tension was recovering, and serum metocurine concentrations were determined using a specific radioimmunoassay. Percentage of paralysis was plotted as a function of log [metocurine] and the data were compared by analysis of covariance. For the normal motor strength patients,  $r = 0.84$ ; for the unaffected arm of the hemiplegic patients,  $r = 0.69$ ; and for the affected arm of the hemiplegic patients,  $r = 0.86$ , all significant at  $P < 0.001$ . The mean plasma metocurine concentrations at 20, 25, 50, 75, and*

*80% paralysis were significantly different for all groups ( $P < 0.001$ ). The regression lines, in turn, did not overlap and were significantly different, each from the other ( $P < 0.005$ ). We were, however, unable to detect any significant deviation from parallelism among the three regression lines. We also measured time to 50% return of single twitch height for each data group as follows (mean  $\pm$  SEM: for NMS patients,  $242 \pm 73$  min; for the unaffected arm of hemiplegic patients,  $116 \pm 60$  min; and for the affected arm of hemiplegic patients,  $59 \pm 36$  min. By ANOVA and the Bonferroni test, each value was different from the other at  $P \leq 0.01$ . We conclude that both the affected arm and the unaffected arm of hemiplegic patients exhibit decreased sensitivity to metocurine, and that the effect of stroke is, even in the long term, global. Thus thumb twitch monitoring in patients with hemiplegia may underestimate the degree of blockade of the muscles of respiration, no matter which side is monitored.*

**Key Words:** NEUROMUSCULAR RELAXANTS—metocurine. BRAIN—stroke.

Patients with upper motoneuron lesions (1,2), thermal injury (3), and liver disease (4); and dogs with disuse atrophy of an extremity (5), have been reported to be resistant to the action of nondepolarizing muscle relaxants. The mechanisms of resistance in these circumstances, though probably interrelated, remain obscure. Several mechanisms have been considered, namely: increased extrajunctional sensitivity to acetylcholine (6); increased numbers of acetylcholine receptors induced by a process known as collateral reinnervation (7); and increased availability of acetylcholine at the receptor site (8).

The longer the duration of injury, the more plau-

sible the first two possible mechanisms become and the easier it is to think purely in terms of changes in the myoneural junction or its neighborhood. Reports by Graham (1), and by Moorthy and Hilgenberg (2), have described resistance to nondepolarizing neuromuscular blockade using indirectly evoked hand twitch tension in patients made hemiplegic by stroke for more than three months. In their report on thermal injury and increased resistance to *d*-tubocurarine, Martyn et al. (3) noted the onset of increased resistance one week or more after significant burn. These investigators examined but then discarded the possibility of altered plasma protein binding of *d*-tubocurarine as an explanation for the increase in resistance. Gronert (5) reported resistance to pancuronium in dog hind legs made atrophic by immobilization for a minimum of 27 days.

The present study was devised to relate serum levels of metocurine (MTC) to the degree of induced muscle relaxation in both the affected and unaffected sides of hemiplegic patients to determine whether the two sides were different from each other and whether

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Table 1. Demographic Data.

	Hemiplegic <sup>a</sup> (n = 8)	NMS patients <sup>a</sup> (n = 8)
Age (yr)	62.4 ± 3.1 <sup>c</sup>	45.1 ± 3.1 <sup>c</sup>
Weight (kg)	73.2 ± 3.3 <sup>b</sup>	72.8 ± 4.4 <sup>b</sup>
Duration of hemiparesis		
Mean (months)	6.6 ± 2.2	
Shortest (hr)	40	
Longest (months)	18	

<sup>a</sup>Values expressed as means ± SEM.<sup>b</sup>No statistically significant differences.<sup>c</sup>By Student's *t*-test, different at *P* = 0.008.

either side differed at all from patients with normal motor strength (NMS). If both sides showed increased resistance to MTC compared to NMS patients, we could reason that the site nearest the injury itself, that is the brain, or some other site more proximal than the myoneural junction, may be involved in the mechanisms causing increased resistance to pharmacologic blockade by nondepolarizing muscle relaxants.

## Materials and Methods

### Experimental Methods

Eight patients with varying degrees of hemiplegia, and eight NMS patients coming to the operating room for a variety of neurosurgical procedures, were studied after we obtained informed consent with institutional review board approval. Demographic data for the sixteen study patients are summarized in Table 1. Operations and diagnoses are noted in Table 2. Anesthesia was induced with thiopental sodium and maintained with nitrous oxide 70% in oxygen 30% plus halothane at an inspired concentration of 0.6–0.8%. One hemiplegic patient received no halothane during the course of the experiment.

Neuromuscular transmission was assessed by measuring indirectly evoked thumb twitch tension with a Grass FT-10 force displacement transducer. For hemiplegic patients, the ulnar nerve was stimulated at both wrists with supramaximal stimuli from a Grass model S8 stimulator in conjunction with a Grass stimulus isolation unit applied to subcutaneous needle electrodes. Using methods previously described by Matteo et al. (9), responses to single stimuli of 0.15 msec duration delivered at a frequency of 0.1 Hz were recorded on a Hewlett-Packard 2-channel recorder. For NMS patients the same procedure and instrumentation was used for one arm.

After induction of anesthesia the patient was initially ventilated by mask. Once a stable baseline limb twitch tension was recorded, MTC, 0.3 mg/kg, was

Table 2. Operations Performed<sup>a</sup>

Hemiplegic patients	7 Carotid endarterectomies (carotid occlusive disease)
	1 (Subdural hematoma) <sup>b</sup>
Patients with normal motor strength	3 Suboccipital craniectomies (acoustic neuroma)
	2 Craniotomies (other tumors)
	2 Anterior cervical laminectomies
	1 Superficial temporal to middle cerebral artery anastomosis (giant aneurysm)

<sup>a</sup>Diagnosis in parentheses.<sup>b</sup>Sedated and intubated in the Neurological Intensive Care Unit. No surgery performed.

administered intravenously and the trachea intubated. As thumb twitch tension returned, blood samples were withdrawn from a radial arterial cannula placed prior to induction of anesthesia. The time from administration of MTC to 50% recovery of initial twitch height was recorded. The samples were heparinized and the serum separated and frozen until analyzed. MTC concentration was determined by specific radioimmunoassay (9).

This radioimmunoassay is a modification of the *d*-tubocurarine assay employed by Horowitz and Spector (10), namely, MTC standards were used (rather than *d*-tubocurarine) at ten times the concentrations used for *d*-tubocurarine, and the incubation time was increased to 48 hr. The sensitivity of this MTC assay is 1 ng/ml, and 50% of antigen–antibody binding is inhibited at an MTC concentration of 2.5 ng/ml. The assay does not vary by more than ± 5% at all concentrations of MTC.

Log serum MTC concentration vs response (% paralysis) curves were constructed from the linear portion of the concentration–response curve between 20 and 80% paralysis for each patient (11). The expected concentrations of MTC at 80, 75, 50, 25, and 20% paralysis were then derived from these curves. The complete sigmoid concentration–response curve could not be determined because the dose of MTC chosen for this study did not cause complete paralysis of the paretic arms and, although the unaffected arms of the hemiplegic patients were all completely paralyzed by 0.3 mg/kg of MTC, there was residual paralysis in these arms when the period of study in each patient was terminated.

### Statistical Analysis

Regression lines for each of the three groups were obtained from the derived values for serum MTC concentration for each patient and were compared by

Table 3. Derived Serum MTC Concentrations ( $\mu\text{g/ml}$ ) for all Patients

% Paralysis	Patient number								Mean $\pm$ SEM <sup>a</sup>
	1	2	3	4	5	6	7	8	
Hemiplegic patients, weak arm ( <i>n</i> = 8)									
80	1.12	1.47	2.27	1.05	2.53	1.52	1.26	1.30	1.56 $\pm$ 0.19
75	1.02	1.36	2.07	0.97	2.12	1.42	1.14	1.22	1.41 $\pm$ 0.16
50	0.70	0.91	1.30	0.66	0.89	1.02	0.70	0.89	0.88 $\pm$ 0.07
25	0.48	0.60	0.81	0.45	0.37	0.73	0.42	0.65	0.57 $\pm$ 0.06
20	0.44	0.56	0.74	0.41	0.55	0.68	0.38	0.61	0.55 $\pm$ 0.04
Hemiplegic patients, "unaffected" arm ( <i>n</i> = 8)									
80	0.35	0.87	1.08	0.88	0.42	0.61	0.69	0.80	0.71 $\pm$ 0.08
75	0.33	0.79	1.0	0.81	0.41	0.57	0.64	0.78	0.66 $\pm$ 0.07
50	0.22	0.48	0.68	0.54	0.32	0.41	0.47	0.65	0.47 $\pm$ 0.05
25	0.14	0.29	0.46	0.35	0.24	0.29	0.34	0.54	0.33 $\pm$ 0.04
20	0.13	0.26	0.42	0.32	0.23	0.27	0.32	0.52	0.31 $\pm$ 0.04
Patients with normal motor strength ( <i>n</i> = 8)									
80	0.34	0.46	0.34	0.42	0.30	0.37	0.35	0.36	0.37 $\pm$ 0.02
75	0.31	0.43	0.31	0.4	0.28	0.35	0.33	0.34	0.34 $\pm$ 0.02
50	0.20	0.35	0.22	0.31	0.2	0.26	0.25	0.25	0.25 $\pm$ 0.02
25	0.13	0.29	0.15	0.24	0.14	0.20	0.19	0.16	0.19 $\pm$ 0.02
20	0.12	0.27	0.14	0.23	0.13	0.19	0.18	0.15	0.17 $\pm$ 0.02

<sup>a</sup>SEM, standard error of the mean.

analysis of covariance. Comparisons among the serum MTC concentrations at various degrees of paralysis for the three data groups, and among the times to 50% recovery of twitch tension were made by performing ANOVA and then applying the Bonferroni multiple comparison test.  $P < 0.01$  was considered significant here (rather than  $P < 0.05$ ), to compensate for diminished rigorousness of the Bonferroni test and to minimize the possibility that differences not statistically significant would be reported as significant.

Adequate serum electrolyte balance was a criterion for induction of anesthesia for all patients, thus  $\text{Na}^+$  and  $\text{K}^+$  were normal in all cases. For patients undergoing craniotomy, we maintained mild hyperventilation under anesthesia ( $\text{PaCO}_2$  ranging between 25 and 30 torr); for patients undergoing carotid endarterectomy, we maintained  $\text{PaCO}_2$  between 30 and 35 torr. Walts et al. (12) were unable to demonstrate a difference in recovery from *d*-tubocurarine-induced neuromuscular blockade in patients hyperventilated to a pH of  $7.62 \pm 0.05$  (mean  $\pm$  SD), and those with normal pH ( $7.36 \pm 0.04$ ). Thus the mild respiratory alkalosis in our patients would not be expected to alter the twitch recovery from MTC blockade.

## Results

Table 3 shows the expected serum MTC concentrations at 20 to 80% paralysis for all patients studied, after the value for MTC concentration was obtained

from each serum sample. The regression lines for the three data groups are presented in Figure 1. The correlation coefficients for the regression lines for the data from each individual patient were all greater than 0.9. The lower value of the correlation coefficients ( $r$ ) for the three lines derived from the pooled data was the result of variation in the slope of the regression line for each individual. When compared by analysis of covariance, the lines were significantly different, each from the other ( $P < 0.005$ ), that is, we were unable to detect overlap of data between groups. We were also unable to detect any statistically significant deviation from parallelism among the three lines. The mean serum concentrations at the various levels of paralysis were significantly different between groups (by the Bonferroni test) at  $P < 0.001$ .

The times to 50% return of single twitch height were as follows (mean  $\pm$  SEM): Hemiplegic arm,  $59 \pm 36$  min; hemiplegic patients' unaffected arm,  $116 \pm 60$  min; and the arm of NMS patients,  $242 \pm 73$  min. By ANOVA and the Bonferroni test all values were different, each from the other, at  $P < 0.01$ .

Because our experimental protocol did not call for use of specific anesthetic agents, we have not excluded the data from one patient (hemiplegic patient number 2) who was given no halothane during the course of the experiment. Retrospectively, the values for MTC concentration at various levels of paralysis (as seen in Table 3) in this patient did not vary by more than one standard deviation from the group

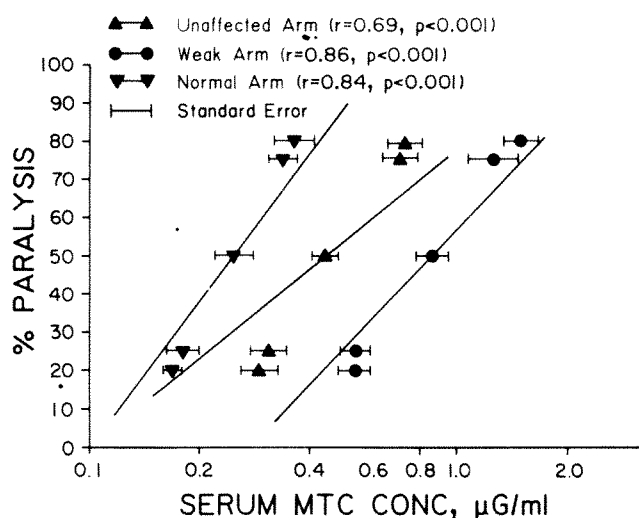


Figure 1. Plot of regression lines for the three data groups. The regression equations are as follows: for NMS patients,  $Y = 128 + 128X$ ; for the unaffected arm of the hemiplegic patients,  $Y = 13.8 + 72.8X$ ; for the weak arm,  $Y = 56.6 + 100X$ . All correlation coefficients are greater than 0 at  $P \leq 0.001$ . The mean MTC concentrations ( $\mu\text{g/ml} \pm \text{SEM}$ ) are plotted to show data fit with the log-linear model.

means for either the unaffected or the hemiplegic arm. Thus we would not expect the different anesthetic technique used in this patient to affect the overall results.

## Discussion

The alteration in sensitivity to MTC in the hemiplegic patient was anticipated on the basis of several recently published reports (1,2,8). We attempted to take those observations a step further by relating the degree of paralysis to serum MTC levels. In previous reports the shortest duration of hemiplegia was three months, and all patients were symptomatically hemiplegic. In our study, the shortest duration of hemiplegia was 40 hr, and one patient had minimal spasticity that did not affect his daily activity to any great degree.

Our data, first of all, show agreement with the previous reports, i.e., on their affected side hemiplegic patients are less sensitive to blockade of neuromuscular transmission by nondepolarizing drugs; and, second, that the sensitivity to MTC on the supposedly unaffected side is greater than on the affected side, but still significantly less than in NMS patients.

How can we account for these differences between hemiplegic patients and nonhemiplegic patients? Differences in blood flow or vasomotor changes, at least during the recovery phase from stroke, can probably be discounted on the basis of a study by Goldberg et al. (13), that showed no difference in blood flow in

the normal and the weak legs in patients one week after onset of hemiplegia. To our knowledge, no regional blood flow data are available with hemiplegia of shorter duration, and thus we cannot exclude the possibility, however remote, that changes in blood flow to the affected side may have altered the response to MTC in our patient who was hemiplegic for only 40 hr.

After a cerebral thrombotic or hemorrhagic event, i.e., stroke, some upper motoneurons degenerate, leaving the lower motoneurons unmodified by cortical impulses. Several investigators (7,14-17) have noted the occurrence of lower motoneuron degeneration after upper motoneuron destruction. McComas et al. (7) believe that after loss of the upper motoneuron, the lower motoneuron can undergo either transsynaptic degeneration, with loss of the lower motoneuron soma and axon, and subsequent atrophy of the motor unit; or restoration of normal or near normal function by increased input from spinal sources, a process known as axonal sprouting, with subsequent collateral reinnervation of muscle fibers. McComas et al. (7) estimate that the process of transsynaptic degeneration takes at least several months, but as few as 48 hr are needed before the "trophic factors" necessary for normal myoneural interaction are depleted. The process of collateral reinnervation may, in turn, take 6-19 months.

In his review of muscle relaxants in infants, Cook (18) cites the importance of the trophic influence of innervation on the maturation of the motor endplate. Brim (6) notes that with denervation of a muscle fiber, membrane sensitivity to acetylcholine spreads beyond the area of the motor endplate. Axelsson and Thesleff (19) have demonstrated this spread 3-6 days after denervation in their experiments on mammalian striated muscle. Fambrough (20) found that the nicotinic receptor inhibitor,  $\alpha$ -bungarotoxin, is bound to extrajunctional sites in muscle made atrophic by immobilization.

To account for the decreased sensitivity to MTC of the weak arm compared to the supposedly unaffected arm in the same patient, we suggest, on the basis of the above discussion, two factors: first, the spread of acetylcholine-sensitive sites beyond the motor endplate after denervation; and second, the increased numbers of receptors produced by collateral reinnervation of individual muscle fibers by surviving lower motoneurons. Furthermore, it has been shown elsewhere, that the process of spread of acetylcholine-sensitive regions can take place in three days and that the effects of denervation can be seen in as few as 48 hr.

Thesleff (21), in his review of the relationship be-



tween skeletal muscle innervation and sensitivity to acetylcholine, and Miledi (22) cite ample evidence that, with loss of the lower motoneuron or the penultimate motoneuron, acetylcholine binding spreads beyond the motor endplate region of the individual muscle fiber. Additionally, direct application of acetylcholine to extrajunctional sensitive regions produces depolarization in a manner similar to the depolarization that occurs at the motor endplate. Paton and Waud (23) rigorously investigated the margin of safety of neuromuscular transmission in cats, and, on the basis of the dose-ratio technique, developed the concept of the presence of a relative excess of acetylcholine receptors, which are blocked more readily by *d*-tubocurarine at high rates of stimulation than at low rates. Using single, indirectly evoked twitches at a frequency of 0.1 Hz, Paton and Waud found that 75% receptor occupancy by antagonist is necessary before any effect of *d*-tubocurarine is seen, and at least 95% receptor occupancy is necessary for complete suppression of the twitch response.

In our experiments we measured twitch recovery and related this response to serum MTC levels. This method was used because it provides the equilibrium condition between blood and extracellular fluid (24,25), and because it helps to eliminate errors caused by individual variations in drug disposition or initial volume of distribution (26). We found that, in order to achieve the same response, MTC levels had to be approximately 2–3 times higher for the affected arm, and 1.5–2 times higher for the supposedly unaffected arm of hemiplegic patients, than those levels measured for the arm of NMS patients. Duvaldestin et al. (25), and Matteo et al. (27), using methods similar to those used in the present study, found that elderly patients (older than 70–75 yr) exhibited no change in sensitivity to nondepolarizing neuromuscular blocking agents compared to younger controls. We should not, therefore, expect a difference in sensitivity to MTC in our older hemiplegic patients because of the differences in age between the two groups.

Adapting Paton and Waud's analysis to our data, we can assume, first of all, that the margin of safety for neuromuscular blockade in hemiplegic patients is unchanged compared to NMS patients, implying that the same proportion of receptors must be occupied by antagonist, MTC, in hemiplegic and in NMS patients to achieve the same effect. Given that receptor number is increased, if the same proportion of receptors must be occupied by antagonist to give the same level of response, then a given serum concentration of antagonist will produce a smaller effect on twitch height. Could the differences in response have been produced by changes in receptor configuration, such

that affinity for antagonist is decreased? The statistical lack of deviation from parallelism of the regression lines for the three data groups provides evidence that altered mechanism of action or change in receptor affinity is not the explanation for our observations. Second, we can assume that the margin of safety in partially denervated muscle is actually decreased (22) compared to normal muscle. This assumption implies that a smaller proportion of receptors must be occupied by antagonist to see a similar decrement in twitch height in hemiplegic patients compared to NMS patients. For a given serum concentration of antagonist, however, we still see a smaller decrement in twitch height in the hemiplegic patient compared to the NMS patient, despite the smaller margin of safety. Thus the increased receptor number overrides any change in the myoneural relationship, and may, in fact, obscure changes in receptor configuration.

What, however, is the explanation for the apparent differences between responses to MTC in the unaffected arm of hemiplegic patients and responses in the arm of NMS patients? By its very nature cerebrovascular disease is a diffuse process. Theoretically, many small areas of ischemia or infarction can occur with transient, nonspecific, or no symptoms (28). Also, with a major intracranial event, i.e., embolism or hemorrhage, the immediate region of the infarct is surrounded by an area of edema, although lumbar spinal fluid pressure is usually elevated only after intracerebral hemorrhage (28). Lastly, the first few hours after a stroke are marked by the greatest intensity of impairment, some of which gradually resolves. Toole (28) attributes the initial transient nature of some aspects of post-stroke neurologic impairment to microembolism or vasospasm. Two studies of nerve conduction velocity in both affected and supposedly unaffected limbs of hemiplegic patients have demonstrated a global decrease in motor units (16) and a bilateral decrease in nerve conduction velocities (17). Furthermore, in the rat, decreased cortical blood flow was demonstrated in the contralateral hemisphere 24 hr after embolization of the internal carotid artery (29), and, in the brains of mongolian gerbils subjected to unilateral cerebral ischemia, morphologic changes were found in the contralateral hemisphere (30).

Thus other investigators, using both human and animal subjects, have been able to demonstrate bilateral neuromuscular impairment after stroke, although more subtly so on the ipsilateral side than on the contralateral. Our results support this concept of bilaterality of effect in a supposedly unilateral event. We suggest four possible reasons for this effect: 1) the possibility of previous, but subclinical, vascular events

on the contralateral side of the brain; 2) the diffuse effect of vasospasm or increased intracranial pressure; 3) the destruction of upper motoneurons innervating ipsilateral muscles via uncrossed pathways; and 4) structural changes in the contralateral hemisphere induced by alterations in cerebral blood flow distribution.

In summary this study quantified the degree of competitive neuromuscular blockade by MTC in both arms of hemiplegic patients, and in one arm of neurologically intact controls. The results show not only that the paretic arm is less sensitive to MTC than the unaffected arm, but also that the unaffected arm is apparently less sensitive than the arm of NMS patients. Possible mechanisms for this phenomenon are discussed. We suggest that twitch monitoring of muscle relaxation in the hemiplegic patient as outlined by Ali and Savarese (31) may underestimate the degree of blockade of the muscles of respiration, not only when applied to the affected arm, but also when applied to the supposedly unaffected arm. Whether this effect is clinically significant, however, needs to be evaluated.

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## Antagonism of Phase II Succinylcholine Block by Neostigmine

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DONATI F, BEVAN DR. Antagonism of phase II succinylcholine block by neostigmine. *Anesth Analg* 1985;64:773-6.

*The neuromuscular effect of neostigmine, 1.25 mg/70 kg, was assessed in 40 adult patients 10 min after cessation of a succinylcholine infusion. The patients had received a thiopental-nitrous oxide anesthetic supplemented by halothane or fentanyl during which they were given at least 5 mg/kg succinylcholine over more than 90 min. Train-of-four monitoring was used. Neostigmine accelerated recovery of neuromuscular function in all patients. The degree of recovery was directly related to the train-of-four ratio, and the results*

*in patients who had received halothane were no different from those who had received fentanyl. The findings are compatible with the hypothesis that phase I block depends upon the presence of circulating succinylcholine and decreases as the latter is cleared, whereas phase II block decreases more slowly. Thus succinylcholine block can be antagonized by neostigmine if enough time is allowed for phase I block to disappear and for a pure phase II block to be present.*

**Key Words:** ANTAGONISTS—neostigmine. NEUROMUSCULAR RELAXANTS—succinylcholine.

Succinylcholine neuromuscular block changes from phase I (depolarizing) to phase II (nondepolarizing) during the intravenous infusion of succinylcholine, especially if prolonged. Several studies have documented potentiation of phase I block and antagonism of phase II block by anticholinesterases (1-3). With the advent of train-of-four monitoring, it became apparent that train-of-four fade could be used to separate phase I from phase II block (3,4). Using a wide range of succinylcholine doses administered by infusion, Lee (4) examined the effect of edrophonium given when first twitch height had recovered to 30-50% of its initial value. He found that the succinylcholine block was antagonized by edrophonium when the train-of-four ratio, T<sub>4</sub>/T<sub>1</sub>, was less than 0.4. However, when T<sub>4</sub>/T<sub>1</sub> was greater than 0.4, edrophonium was followed either by potentiation of the block or no change. The patients in Lee's study had received relatively small doses of succinylcholine, and edrophonium was probably given very shortly after cessation of succinylcholine infusion.

In clinical practice, the need to antagonize succinylcholine block does not arise unless large doses have been given and some time has been allowed for

spontaneous recovery. This study was designed to mimic the clinical situation. After prolonged infusions, a 10-min recovery period was allowed before a small dose (1.25 mg) of neostigmine was given with atropine. The effect of the anticholinesterase was measured in patients who received halothane and in those who had a nitrous oxide-narcotic anesthetic, because halothane can affect the characteristics of phase II block (5).

### Methods

The procedure was approved by the Hospital Ethics Committee. After giving informed consent, 40 healthy adults of ASA status I or II, without known or suspected neuromuscular, hepatic, or renal disease, were studied during elective surgical procedures. They were randomly allocated to two groups. All patients received similar premedication with an oral benzodiazepine, a narcotic, or both, and an anticholinergic agent. Anesthesia was induced with 3-5 mg·kg<sup>-1</sup> thiopental and maintained with 70% nitrous oxide in oxygen supplemented, in one group, with 0.5-1% halothane (inspired) and, in the other group, with 0.25 mg fentanyl after induction with approximately half-hourly increments of 0.1 mg. Tracheal intubation was performed in all patients after the administration of relaxant as described below, and they were ventilated to maintain normocapnia, which was assessed by measurement of end-tidal carbon dioxide concentration (Hewlett Packard HP capnograph). The arte-

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rial pressure and electrocardiogram were monitored in all patients.

The ulnar nerve was stimulated supramaximally with subcutaneous needle electrodes at the elbow. Four square-wave impulses of 0.2-msec duration and 2-Hz frequency were administered every 12 sec using a Grass S48 stimulator and SIU5 Isolation Unit. The hand and forearm were immobilized in a splint. The force of contraction of the adductor pollicis muscle was measured with a Grass FT10 force-displacement transducer, and the response was recorded on a Grass-Polygraph pen and ink recorder. The skin temperature above the adductor pollicis was monitored and maintained greater than 32°C.

After establishment of a stable base line, a 0.4% succinylcholine infusion was started using an IMED constant infusion pump, initially at a rate of 10–16 mg·min<sup>-1</sup>, to produce at least 90% depression of the first twitch of the train-of-four. At this point the trachea was intubated. The infusion rate was then adjusted to maintain the height of the first twitch (T1) at 10–15% of the preinfusion value. With the approach of the end of the operation the infusion was stopped and spontaneous recovery allowed to occur for 10 min. If the ratio of the fourth to the first twitch (T4/T1) of the train-of-four was more than 0.7, recovery was considered complete and the patient was excluded from the study. If T4/T1 was 0.7 or less, neostigmine, 18 µg/kg (1.25 mg/70 kg) was given with atropine, 0.6 mg. A second dose of neostigmine was given 3 min later if required. All patients were monitored until T4/T1 became greater than 0.7.

Assessment of recovery was made 3 min after the first dose of neostigmine. A recovery index for the first twitch tension (RI<sub>T1</sub>) was defined as follows:

$$RI_{T1} = \frac{T1 \text{ Post} - T1 \text{ Pre}}{T1 \text{ Final} - T1 \text{ Pre}}$$

where T1 Post, T1 Pre, and T1 Final are first twitch tensions 3 min after neostigmine, at the time neostigmine was given, and when full recovery was attained, respectively. Thus a recovery index of 1 indicates full recovery, 0 means no recovery, and a negative value implies potentiation of the block. A recovery index for train-of-four ratio (RI<sub>TOF</sub>) was defined in a similar manner:

$$RI_{TOF} = \frac{(T1/T4)_{\text{Post}} - (T1/T4)_{\text{Pre}}}{1 - (T1/T4)_{\text{Pre}}}$$

where (T1/T4)Post and (T1/T4)Pre are train-of-four ratios 3 min after neostigmine and at the time neostigmine was given, respectively. In order to account for spontaneous recovery that would have occurred

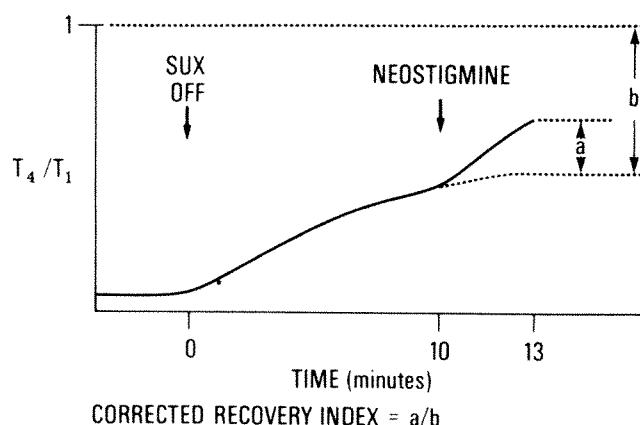


Figure 1. Calculation of corrected recovery index.

in the absence of anticholinesterase, a corrected recovery index (CRI) is defined as follows:

$$CRI = \frac{(T1/T4)_{\text{Post}} - (T1/T4)_{\text{ext}}}{1 - (T1/T4)_{\text{ext}}}$$

where (T1/T4)<sub>ext</sub> is the train-of-four ratio obtained by extrapolation of spontaneous recovery data to 3 min after administration of neostigmine (Fig. 1).

Data are presented as recovery indices as a function of train-of-four ratio at the time neostigmine was given, i.e., 10 min after succinylcholine infusion was stopped. Regression analysis was performed using least mean squares, *t*-test was applied to slopes, and a *P* value of less than 0.05 was considered significant.

## Results

Patient demographic data, duration of succinylcholine infusions, and total dose given are presented in Table 1. There were no statistically significant differences between the two groups of patients. No patients received succinylcholine for less than 90 min, and the smallest total dose given was 5 mg/kg. All patients had a train-of-four ratio of zero at the end of the infusion.

Recovery index for the first twitch (RI<sub>T1</sub>) was plotted against train-of-four ratio (Fig. 2). In all patients the RI<sub>T1</sub> was greater than zero, which indicates antagonism of the block. The RI<sub>T1</sub> increased with train-of-four ratio, so that recovery was significantly better when train-of-four ratio was large. No differences were found between patients who received N<sub>2</sub>O–halothane and N<sub>2</sub>O–fentanyl. Similar observations apply to the recovery index for train-of-four ratio (RI<sub>TOF</sub>) (Fig. 3). When spontaneous recovery of the train-of-four was subtracted from the recovery index, a corrected recovery index was obtained (Fig. 4). Again, no poten-



Table 1. Demographic and Succinylcholine Data for the Two Groups of Patients

	Patient data		Succinylcholine data	
	Age (yr)	Weight (kg)	Duration of infusion (min)	Total dose (mg/kg)
Group 1—Fentanyl, (9M, 11F)				
Mean	60	68	160	15.4
SEM	3.6	2.2	7.6	1.1
Range	26-81	48-86	90-225	10-28
Group 2—Halothane, (9M, 11F)				
Mean	56	68	131	13.3
SEM	4.1	2.9	9.6	1.0
Range	21-79	42-102	90-223	5-22

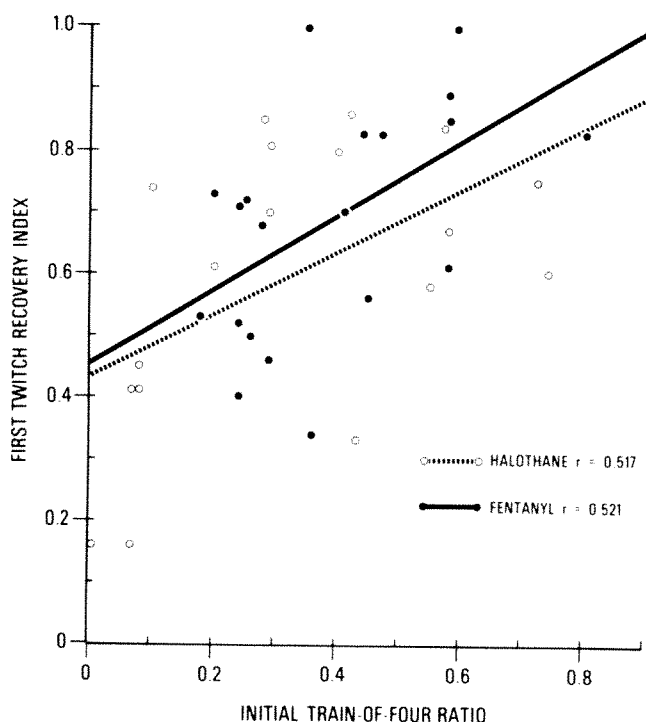


Figure 2. First twitch tension recovery index as a function of train-of-four ratio at the time of neostigmine administration.

tiation was observed, recovery improved as train-of-four ratio increased, and no difference between the two anesthetic techniques was detected.

## Discussion

This study suggests that succinylcholine phase II block can be antagonized with an anticholinesterase, provided that fade of the train-of-four has been demonstrated during the infusion, and that spontaneous recovery of neuromuscular activity has been allowed to take place for at least 10 min after cessation of the

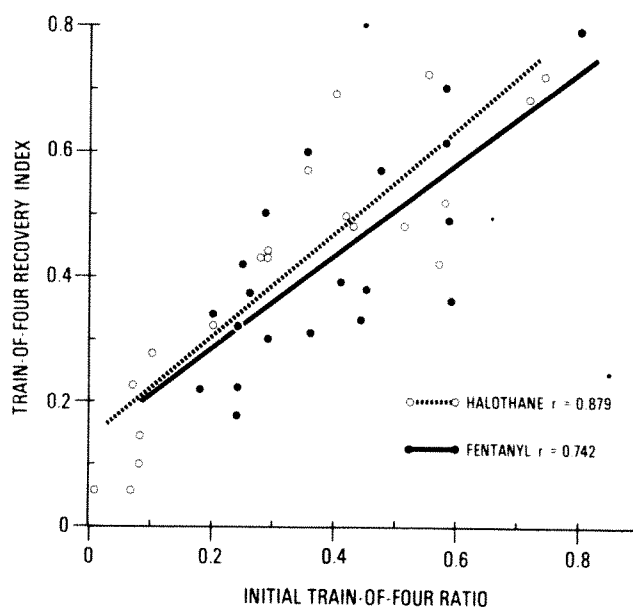


Figure 3. Train-of-four recovery index as a function of train-of-four ratio at the time of neostigmine administration.

succinylcholine infusion. Neostigmine produces more effective recovery when spontaneous recovery of the train-of-four is large. Halothane, which accelerates the onset of phase II block, does not interfere significantly with its antagonism by neostigmine.

These data seem to contradict previous results. Lee (4) used edrophonium after a succinylcholine infusion, when first twitch height reached 30-50% of the initial value, and found predictable antagonism only when the train-of-four ratio was less than 0.4. In the current study, neostigmine antagonism was improved by increasing train-of-four ratios. This apparent contradiction probably does not arise from the different anticholinesterases used, but from differences in methods. Lee administered the anticholinesterase at a fixed level of first twitch height recovery (30-50%), whereas in the present study neostigmine was given at a fixed time after stopping the infusion. When the total doses of succinylcholine are as low as 0.5 mg/kg of succinylcholine, some patients must have been given edrophonium very soon after cessation of succinylcholine infusion, because the recovery time depends directly on the total dose administered (6). In this situation, a train-of-four ratio greater than 0.4 probably indicates phase I block. On the other hand, all our patients received more than 5 mg/kg of succinylcholine, and all of them exhibited the characteristics of phase II block during the infusion. In this context, a train-of-four ratio greater than 0.4, 10 min after cessation of the infusion, indicates a recovering phase II block. The effect of neostigmine was greater

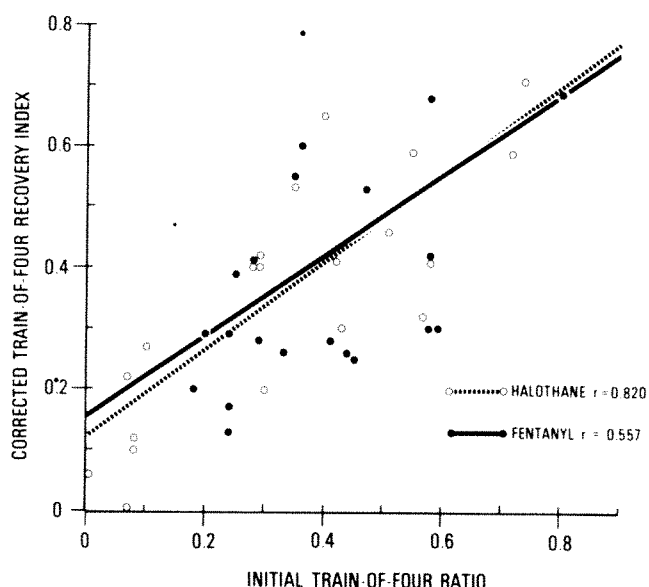


Figure 4. Train-of-four recovery index corrected for anticipated spontaneous recovery, at the time of neostigmine administration.

with less intense levels of succinylcholine block, as it is with the antagonism of nondepolarizing muscle relaxants (7).

Anticholinesterases have been found to have unpredictable effects in patients who received succinylcholine concurrently (8,9) or in individuals with atypical plasma cholinesterase (10). In this study, the antagonistic effect of neostigmine was complete and predictable. These seemingly contradictory results can be reconciled by assuming that phase I block has a short onset and rapid offset, and depends on the presence of succinylcholine at the neuromuscular junction that parallels the plasma succinylcholine concentration very closely. Phase II block, however, takes a longer time to develop but may outlast the presence of succinylcholine. According to this hypothesis, patients who metabolize succinylcholine normally will remain with a pure phase II block shortly after discontinuation of the drug, and neostigmine will be an effective antagonist. Whereas patients with abnormal pseudocholinesterase will exhibit some phase I block concurrently with phase II block, which will persist even after cessation of the succinylcholine infusion,

and anticholinesterase may not be effective in reversing the block. Thus neostigmine may be used to antagonize succinylcholine block whenever there is clinical evidence of pure phase II block: train-of-four fade has been documented during the infusion; a reasonably long spontaneous recovery period has been allowed after cessation of succinylcholine administration (a duration of at least 10 min, which is about 3 times succinylcholine half-life in normal patients (11), appears to be adequate); and the doses of succinylcholine required for relaxation are compatible with the presence of a normal plasma cholinesterase.

Using these criteria we have observed rapid return of spontaneous ventilation after antagonism of phase II block with neostigmine. However, before stopping controlled ventilation, the clinician must be convinced that the patient can sustain spontaneous breathing, as he does after antagonizing the competitive relaxants.

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## Atracurium-Receptor Kinetics: Simple Behavior from a Mixture

Yoshikiyo Amaki, MD, Barbara E. Waud, MD, and Douglas R. Waud, MD, DPhil

AMAKI Y, WAUD BE, WAUD DR. Atracurium-receptor kinetics: simple behavior from a mixture. *Anesth Analg* 1985;64:777-80.

*The apparent atracurium-receptor dissociation constant was assayed at the end-plate region of isolated guinea pig muscles. In a parallel series of experiments, the ED<sub>50</sub> for producing neuromuscular block in the lumbrical muscle was also determined. The ratio of these two values was similar*

*to the ratio found with classical competitive neuromuscular blocking agents like d-tubocurarine or pancuronium. We conclude that the commercial preparation of atracurium, though a mixture containing isomers of different configurations, behaves kinetically in a manner indistinguishable from what would be expected from a single substance.*

**Key Words:** NEUROMUSCULAR RELAXANTS—atracurium.

Atracurium, a recently introduced neuromuscular blocking agent (1-3), has been designed to be relatively unstable chemically and therefore to have a shortened half-life. The structure of atracurium (Fig. 1) includes ester bonds that are susceptible to hydrolysis as in succinylcholine, but the ester moiety is arranged such that the carbonyl carbon can also facilitate breakage of the bond between the quaternary nitrogen and the carbon atoms between that nitrogen and ester bond.<sup>1</sup> The price paid for this elegant ar-

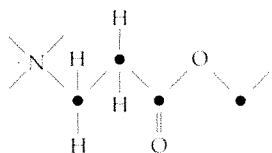
rangment is a rather complicated molecule. In particular, there are four asymmetric sites in the molecule (asterisks in Fig. 1), and thus 2<sup>4</sup> or 16 possible steric isomers. Actually, because the molecule is symmetrical, only 10 of these are different; but the synthesis of atracurium still results in a mixture of molecular configurations. It is apparently impractical to purify one single isomer (all the variants would be expected to have similar physiochemical properties). The result is that, as noted in the package insert, the preparation available chemically is a mixture (with a preponderance of the configuration indicated in Fig. 1).

A mixture of compounds per se presents no serious kinetic problem. When several competitive antagonists act at one receptor, the mixture behaves as though it were a single drug at a normalized concentration

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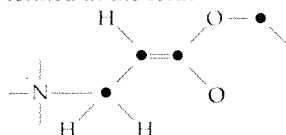
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<sup>1</sup>The key part of the molecule is the structure

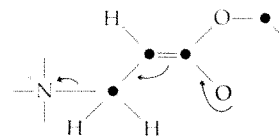


The presence of the carbonyl moiety (C=O) next to the —CH<sub>2</sub>— means that the protons can leave the latter more readily because the molecule can "park" the electron left behind on an atom, oxygen, which, because of its electronegativity, will store the negative charge more readily than carbon. (The pK<sub>a</sub> of acetone, CH<sub>3</sub>C(=O)CH<sub>3</sub>, is 20; that of methane is 40. In other words, the presence of the oxygen in the former compound lets hydrogen ions leave 10<sup>20</sup> times more readily.)

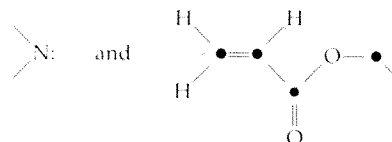
Thus the presence of that C=O group implies that some of the molecules will be formed in the form



Although the proton can return and reverse the process, a more interesting alternative is the electron flow



leading to



i.e., a fracture in the molecule. This is the "Hoffman elimination" referred to in the atracurium literature. Incidentally, the reason atracurium cannot be mixed with a thiopental solution is that the alkalinity of the latter will increase the likelihood a proton comes off the carbon atom to initiate breakdown.

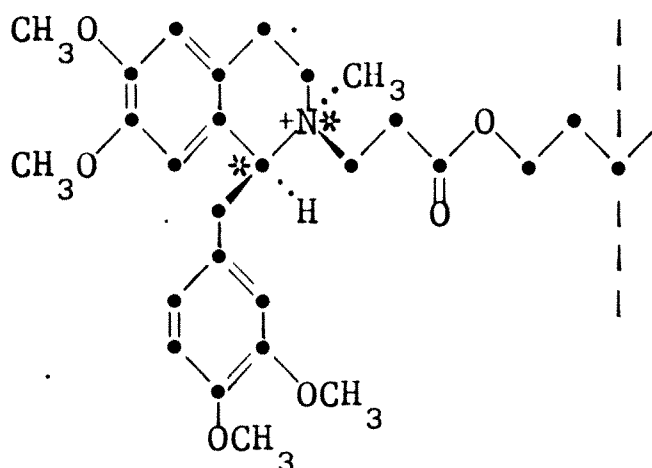


Figure 1. Atracurium. Only one-half of the molecule is shown fully (the vertical dashes indicate the mid-plane of the molecule). The asterisks label asymmetric centers. The particular configuration shown is that said to predominate in the commercial preparation Tracrium.

equal to the sum of the normalized concentrations of all the components, i.e.,

$$C_{\text{equiv}} = \sum_i C_i$$

where  $C_i$  is the actual concentration of the  $i$ th component of the mixture divided by the dissociation constant,  $K_i$ , for the reaction of that component with the receptor (4), i.e.,

$$C_i = [\text{component } i]/K_i.$$

Thus one can treat the mixture as if it were a pure substance.

Until recently, the observed kinetics of the reaction of neuromuscular blocking agents with the end-plate receptors has been consistent with the classical model when the measurements were done under the tight experimental control of an *in vitro* system (5). However, in a series of elegant studies, Taylor et al. (6,7), measuring simultaneously both binding to acetylcholine receptors and their activation, have demonstrated in cultured cells that the situation is not that of the simple one-to-one reaction underlying the classical model. In particular, they found binding to two sites, both of which have to be activated by the transmitter to open the receptor-associated membrane channel, and only one of which therefore need be blocked by a curariform drug. This is consistent with the results of structural studies (8) of the acetylcholine receptor-channel complex, a structure composed of five monomers; two alike, both with binding sites for the transmitter (or the blocking agent). Furthermore, as Taylor et al. show by direct measurement, these two

sites do not behave identically (as might be expected from the asymmetrical environment in which they lie). The implication is that the classic model for kinetics at the acetylcholine receptor might be expected to break down in some cases.

This indeed seems to be the case. When pairs of neuromuscular blocking drugs were examined under close experimental control, some combinations produced a greater degree of block than would be expected on the basis of the classic model (9,10). Such atypical behavior had already been suspected in clinical studies (11,12). Mixtures of drugs are more likely to show atypical behavior than are pure compounds. The reason is that one of a pair of drugs may bind selectively to one of the two receptor drug-binding subunits, while the second drug favors the other subunit. This amounts to a two-pronged attack, because only one subunit has to be occluded to inactivate that particular receptor-channel complex (6). A single compound obviously cannot go selectively for both sites at once.

The question is whether or not the commercial mixture of atracurium is of such a composition that it exhibits atypical kinetics. We have therefore done a standard kinetic assay on the commercial preparation and a parallel assay of its ability to block the indirectly elicited twitch response. Comparison of results of the two assays will indicate whether there is enough atypical behavior to be clinically appreciable.

## Methods

Two types of assays were performed, both on isolated guinea pig lumbrical muscles at 37°C in Krebs' solution of the following composition (mM):  $\text{Na}^+$  138,  $\text{K}^+$  5.9,  $\text{Cl}^-$  123,  $\text{Ca}^{2+}$  1.26,  $\text{Mg}^{2+}$  1.22,  $\text{H}_2\text{PO}_4^-$  1.2,  $\text{SO}_4^{2-}$  1.22,  $\text{HCO}_3^-$  25, lactate 2.52, plus glucose 2.08 g/L, and bubbled with 95%  $\text{O}_2$ /5%  $\text{CO}_2$ .

In one set of experiments, depolarization of the end-plate region by bath-applied carbachol was monitored with the moving fluid electrode technique (5,13). After a control dose-response curve was established, curves in the presence of atracurium (0.05–0.2  $\mu\text{M}$ ) were determined; and then, after washout of the blocking agent, a second set of control values was obtained to confirm reversibility. The shift of the dose-response curve in the presence of the atracurium was then used to estimate the apparent antagonist-receptor dissociation constant as described previously (14).

In the second assay (15), the muscle was removed with its nerve attached and activated by application of supramaximal 0.1-msec pulses to the nerve every 10 sec. The resulting isometric twitch responses were



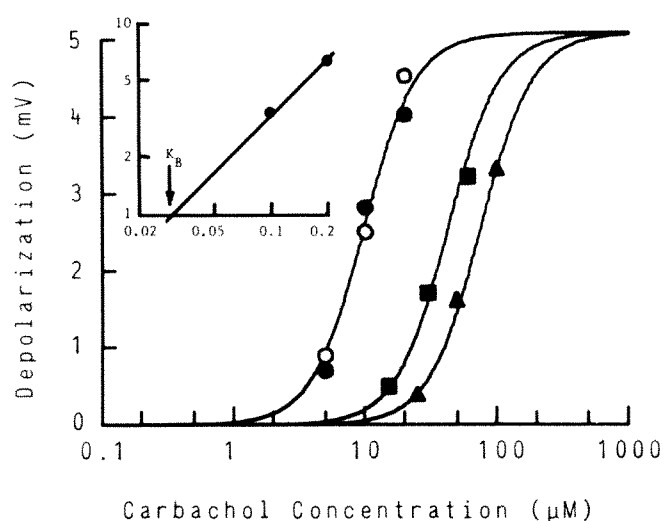


Figure 2. Example of an assay to measure atracurium-receptor dissociation constant. (Main panel) Experimental results; full and open circles, control values before and after atracurium added; squares and triangles, values in the presences of 0.1 and 0.2  $\mu\text{M}$  atracurium; curves, from a least squares fit of the classical model to the observations (14). (Inset) Associated "Schild plot", ordinates, dose-ratios minus 1; abscissae, antagonist concentrations ( $\mu\text{M}$ ) yielding those values. Line drawn with unit slope. Intercept (arrow) indicates a dissociation constant of 0.03  $\mu\text{M}$  for the atracurium in this particular experiment.

recorded on a chart recorder. After about 0.5 hr for equilibration in vitro, graded doses of atracurium were added cumulatively to establish the dose-response relationship for block of the indirect twitch. The  $\text{ED}_{50}$  for twitch depression was obtained from a least squares fit of the function

$$Tw = 1 - B^S / (B^S + K^S) \quad (1)$$

(where  $Tw$  is the twitch response,  $B$  is the concentration of antagonist,  $S$  reflects steepness of the relationship, and  $K$  is the  $\text{ED}_{50}$  we seek, a function chosen empirically to fit the s-shaped relationship found in such assays).

## Results

Figure 2 gives an example of an assay to measure the apparent drug-receptor dissociation constant. Atracurium shifts the dose-response curve to the right in the classical fashion, and the associated "Schild plot" (16) is consistent with the slope of unity expected for competitive kinetics. Statistical analysis (14) of the results in Figure 2 gave an estimate of 0.904 ( $\pm 0.145$  SEM) for the parameter corresponding to the slope of the Schild plot and one of 0.030 ( $\pm 0.002$  SEM) micromolar for the drug receptor dissociation constant. All such experiments (eight preparations) gave an overall value of 1.22 ( $\pm 0.12$  SEM) for the Schild pa-

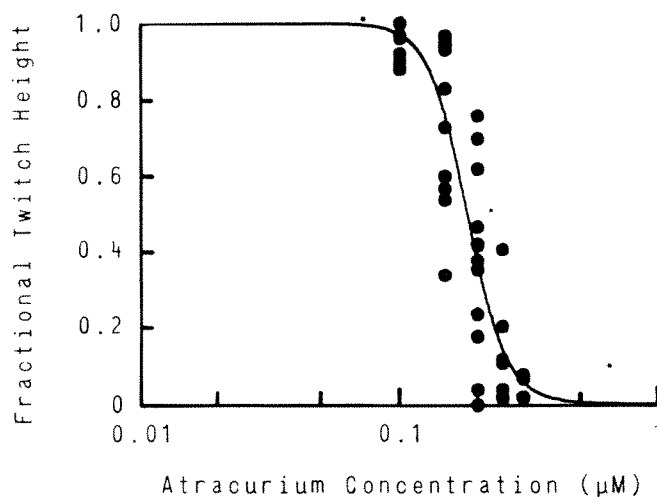


Figure 3. Summary of results of the assay on the indirect twitch response. Ordinates, fractional twitch responses; abscissae, concentrations of atracurium. Curve represents least squares fit of equation (1) to the results. Data from 13 preparations.

rameter and 0.0271 ( $\pm 0.0017$  SEM) micromolar for the dissociation constant.

Figure 3 gives the results of the assay on the indirect twitch response. The curve represents the least squares fit and has an  $\text{ED}_{50}$  estimated at 0.186 ( $\pm 0.008$  SEM) micromolar (13 preparations). The steepness parameter ( $S$  in Equation (1)) was 7.61 ( $\pm 0.63$  SEM) in the usual range of such assays.

## Discussion

The results in Figure 2, and indeed in all such experiments, look like typical competitive kinetics as seen with *d*-tubocurarine or pancuronium (compare Figures 3 and 5 of an earlier report (17)). Similarly, the relationship summarized in Figure 3 is comparable to that usually seen with competitive antagonists. The key issue, however, is whether the two sets of results are consistent with each other. The apparent atracurium-receptor dissociation constant was 0.0271  $\mu\text{M}$ . The  $\text{ED}_{50}$  for blocking the indirect twitch response was 0.186  $\mu\text{M}$ . This latter value corresponds to a fractional receptor occlusion of 0.87,<sup>2</sup> a value comparable to the values of 0.89, 0.86, 0.86, and 0.88 seen with fazadinium, pancuronium, *d*-tubocurarine, and vecuron-

<sup>2</sup>Fractional receptor occlusion  $y_B$  by a drug at concentration  $B$  and with a drug-receptor dissociation constant  $K_B$  is given (4) by

$$y_B = B / (B + K_B).$$

In the present case  $K_B$  is 0.0271 micromolar, and  $B$  is 0.186 micromolar, so

$$y_B = 0.186 / (0.186 + 0.0271) = 0.872.$$

ium, respectively (15). Thus the atracurium mixture shows kinetic behavior indistinguishable from that of a single compound. If the mixture had been such as to contain components that showed widely varying affinity for the two receptor subtypes, then one might have seen block of the twitch response at lower relative concentrations than those needed with a pure substance.

We conclude, therefore, that although use of a preparation that consists of a mixture of compounds had the potential for atypical kinetic behavior, the components present in commercial atracurium fortuitously happen to behave just like a single drug. Thus the anesthesiologist can expect that use of the commercial preparation as if it were a single drug is heuristically reasonable and should not lead to unexpected bizarre responses.

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## Electrophysiologic Evidence for Involvement of the Pituitary Region in Opiate Analgesia

Ad Trouwborst, MD, PhD, Wilhelm Erdmann, MD, PhD, Hisashi Yanagida, MD, PhD, and Guenter Corssen, MD, PhD

TROUWBORST A, ERDMANN W, YANAGIDA H, CORSEN G. Electrophysiologic evidence for involvement of the pituitary region in opiate analgesia. *Anesth Analg* 1985;64:781-5.

*In the past, various reports have discussed the relationship between the pituitary and analgesia. The purpose of the present study was to explore the possible role of the pituitary region in the mediation of pain by opioids. Tooth pulp evoked potentials recorded from primary somatosensory cortex and from the pituitary region of rabbits were recorded before and*

*after an injection of opiates. Tooth pulp evoked potentials recorded from the primary somatosensory cortex were markedly inhibited after admission of fentanyl, while the tooth pulp evoked potentials recorded from the pituitary region were facilitated. It is concluded that the pituitary region plays a role in the mediation of pain and that this area is involved in the mechanism of opiate analgesia.*

**Key Words:** ANALGESICS—fentanyl. BRAIN—pituitary.

Many studies suggest an influence of opioids on different levels in the central nervous system such as the medial and intrathalamic nuclei, medulla, brainstem, and segmented dorsal horn areas. It seems that the action of exogenous opiates may be both directly at the spinal level and at higher levels of the central nervous system as well. Microelectrophoretic administration of opiates in different areas of the central nervous system have revealed depressant as well as excitatory actions upon single unit discharge rates; however, other studies have shown depressant effects of narcotic analgesics upon neuronal activity at the spinal level (1-7). The existence of high levels of  $\beta$ -endorphins and enkephalin in the pituitary region (PR) suggests that this area may also be involved in mediating the effects of narcotic analgesics (8,9). Many papers suggest that hypophysectomy in animals can affect pain produced by a variety of stimuli, and that after removal of the pituitary a naloxone-induced hyperalgesia cannot be observed (10-12). The purpose of the present study was to determine the electrical activity of the pituitary region and the influence on it of an exogenous opiate in comparison to the re-

sponse in the primary somatosensory cortex (PSC), measuring tooth pulp evoked potentials (TPEP) in both areas.

### Methods

Seven male adult New Zealand white rabbits, weighing 2.5-3 kg were used in the experimental procedure and an additional three rabbits were used for the pilot studies. Under fluanison (fluoro-butyrophenon) fentanyl anesthesia, two silver bone screws were screwed through the skull and brought into direct electrical contact with the primary somatosensory cortex, one on each side. They served for bipolar registration of the electrical activity of the PSC. An additional bone screw was introduced into the skull in a midline position. This made no contact with the brain and served as a ground. Another bone screw was inserted into the bone at the nasal-inion line as a reference electrode for the hypophyseal registration. A 16-gauge epidural stainless-steel needle containing a Teflon-coated wire electrode, with a free tip of 200- $\mu$  diameter, was advanced through the right nostril into close proximity of the nasal septum. Progression of the needle was carefully monitored by bi-plane fluoroscopy until the needle tip had reached the center of the upper part of the sella turcica. The wire electrode was kept in this position in the pituitary region (PR) as the needle was gently withdrawn. The connecting wire was then passed subcutaneously to the top of the skull. The

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correct positioning of the PSC electrodes and the electrodes in the PR were thereafter assured by x-ray and, after the experiment, correct positioning was again assured macroscopically.

To introduce the pain stimulus electrodes, small holes were drilled through the enamel and dentine of both maxillary incisors to a depth of about 0.5 mm, through which two self-threading pins were inserted and embedded into the tooth pulp after destruction of the surrounding gingival structures. The latter was performed to prevent artefacts in tooth pulp evoked potential (TPEP) recordings. The pins were soldered to insulated connecting wires that were passed subcutaneously to the front of the skull. The exposed junctions of the dental pins and steel wires were insulated from the oral cavity by self-curing dental acrylic. All bone screws and subcutaneously placed wire connections to the stimulating electrodes and hypophyseal electrodes were soldered to a multichannel plug that was fixed by dental acrylic to the skull bone. Care was taken to ensure that all noninsulated connection points and open ends of screws were insulated by the acrylic.

After the implantation of the electrodes, the rabbits were allowed to recover for at least 48 hr. TPEP recording sessions were conducted with the unsedated rabbit placed in a restraining box in the upright position. All experiments were performed between 4:00 PM and 2:00 AM because naloxone is maximally active in reducing latencies during this period of the day (23).

EEG and evoked potential responses were recorded from PSC and PR, employing a Grass polygraph recorder equipped with an A-C amplifier (Fig. 1). A Hewlett-Packard storage oscilloscope was used for continuous monitoring of electrical activity, TPEP, and the tooth pulp electrical stimulation.

For tooth pulp stimulation, monophasic square waves of 0.3 msec duration and 10 V were generated by an electrical stimulator (Grass S-20) equipped with a modified stimulus isolation unit, and delivered at 3.0-sec intervals. Analysis times were 100 and 300 msec. The responses to 45 consecutive stimuli administered to each animal were averaged, employing a Hewlett-Packard clinical averager. Amplitudes were measured from the base to the peak of each component wave. Latencies were measured from the onset of the stimulus to the peak of each component wave.

## Experimental Procedure

After positioning the animal in the restraining box in the upright position, the multichannel plug was connected to the recording and stimulating equipment.

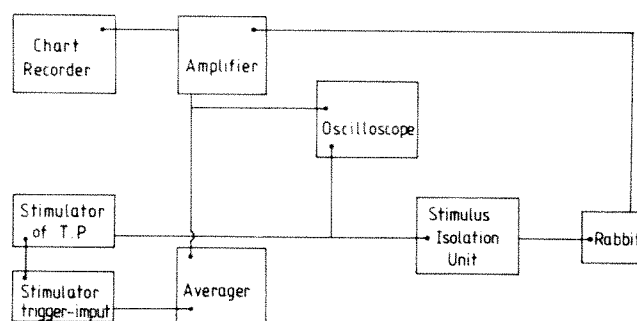


Figure 1. Schematic of the recording system.

Primary somatosensory cortex and hypophyseal spontaneous electrical activity was recorded until steady-state recording was achieved for at least 30 min, while movements in the room (and throughout the whole experiment) were reduced to a minimum. An initial pilot study was performed in three different rabbits. Different amounts of fentanyl (0.005 mg/kg; 0.01 mg/kg; and 0.015 mg/kg) were injected intramuscularly and the TPEP was again recorded. The effects of fentanyl in the pilot study are shown in Table 1; 0.01 mg/kg produced an adequate effect within 10 min. Thus in the remainder of the study, a dose of 0.01 mg/kg fentanyl was administered intramuscularly, and the first TPEP was recorded 10 min after injection. All experiments were repeated after 24 hr to prove reproducibility.

After all experiments had been completed, the rabbits were anesthetized and the brain removed to ensure that the electrodes were correctly positioned. The Wilcoxon matched-pairs signed rank test was used for determination of statistical significance (13).

## Results

The animals withstood all phases of the experiment well, and there was no indication of behavioral or physiological changes. In particular, purposeful body movements, as well as rejection behavior, anger, and appetite remained unchanged. Only during stimulation of the tooth pulp was a very quick opening and closing of the mouth observed unaccompanied by vocalization.

At the end of the experiment, when the animals were returned to their cages, they reverted to normal behavioral patterns.

### TPEPs of the PSC

The electrical stimulus applied to the tooth pulp produced a triphasic response of TPEP in the PSC in all animals (Table 2). The tracing showed, after an



**Table 1.** Changes of TPEP Amplitudes (in % from Control) in the PSC and PR at Different Doses of Fentanyl and at Different Time Intervals ( $n = 3$ )

Fentanyl (mg/kg)	Primary somatosensory cortex			Pituitary region		
	Min after injection					
	5	10	15	5	10	15
0.005	- 8.2	- 16.1	- 14.5	+ 6.1	+ 17.4	+ 14.7
0.01	- 11.4	- 24.7	- 22.3	+ 10.8	+ 25.3	+ 23.5
0.015	- 12.6	- 24.6	- 23.3	+ 11.4	+ 24.6	+ 24.1

initial steep negative deflection, two positive deflections. The amplitude of the second positive wave, appearing approximately 30 msec after the stimulation of the tooth pulp, corresponded to the intensity of the stimulation of the tooth pulp. The averaged amplitude was 21  $\mu$ V. After injection of fentanyl, the second positive wave showed a statistically significant decrease in amplitude averaging 24% ( $SEM \pm 2.9$ ;  $P < 0.05$ ) to an average voltage of 16  $\mu$ V (Fig. 2, left).

#### TPEPs of the PR

The electrical stimulus to the tooth pulp produced a polyphasic response in TPEPs in the PR with a positive deflection followed by a marked negative deflection and, thereafter, a dominant positive wave (Table 2). The amplitude of this dominant positive wave appeared approximately 20 msec after the stimulus, and was closely related to the intensity of the stimulation of the tooth pulp. The averaged amplitude was 27  $\mu$ V.

After injection of fentanyl, the amplitude of this positive wave increased statistically significantly in all animals averaging 25% ( $SEM \pm 5.7$ ;  $P < 0.05$ ) to 33.5  $\mu$ V (Fig. 2, right); this was contrary to the response of the PSC where the original response decreased after injection of fentanyl.

In the pilot study of three animals, after the measurements had been completed, the pituitary electrode was moved forward from the center position to the direction of the hypothalamus and out of the sella region. The evoked potentials recorded via this electrode system disappeared and could only be partially restored by a fourfold increase in the intensity of the stimulus of the tooth pulp.

#### Discussion

In the present study, tooth pulp evoked potentials were chosen for the measurement of acute experimental pain. Electrophysiological and anatomic studies have demonstrated that tooth pulp afferents con-

sist exclusively of A-delta and C-fibers (14-16). The amplitude of TPEPs in the primary somatosensory cortex (PSC) have been reported to be proportional to the stimulus intensity, and this reflects the sensory magnitude in a quantitative manner (17-22).

In this study, the effects of an opiate were investigated to determine a possible role of the pituitary region (PR) in opiate analgesia. Recent publications have supported the concept that the hypophysis might play a major role in pain perception. In these reports it was shown that the endorphin antagonist, naloxone, produces hyperalgesia in animals with an intact hypophysis (10,12,23-25), though in hypophysectomized animals this effect is absent (10,12). Severe stress also produces analgesia that may also be associated with a hypophyseal increase of endorphin activity (26-29), though hypophysectomy can block this "stress-induced analgesia" (11,12,30). These findings draw attention to interference of the hypophysis with pain via some type of endorphinergetic mechanism.

Our new finding that fentanyl and, presumably, other opioids have opposite effects on the TPEPs of the PR and of the PSC, suggests a possible inhibitory effect of the PR on the response of the sensory cortex to painful stimuli, a mechanism that may be influenced by opiates. The effect of opioids could be mediated via neuromodulation, or it could represent interference with neurotransmission via enkephalinergic neurons involved in one of the pain pathways situated in, or near, the PR.

Fine varicose enkephalinergic nerve fibers have been demonstrated on the perimeter of the neural lobe of the hypophysis and in the pituitary stalk, and lesioning experiments show the presence of enkephalinergic cell bodies in the magnocellular nuclei of the hypothalamus with projections into the pars nervosa of the pituitary (31). In addition, opiate receptors have been demonstrated in the pituitary gland (32). The roles of these enkephalinergic neurons and opiate receptors remain undefined. It has been suggested, however, that they are also involved in the modification of the neurohypophyseal neurosecretion (33).

Table 2. TPEP recordings ( $\mu$ V) of the Original Experiments in the Pituitary Region (a) before and (b) after Injection of Fentanyl

Number	Primary somatosensory cortex			Pituitary region		
	a	b	% change	a	b	% change
1	18.37	13.76	-25.1	27.01	33.55	+24.2
2	18.31	13.27	-27.5	17.48	23.72	+35.7
3	16.91	13.87	-18.0	9.95	13.78	+38.5
4	19.85	12.90	-35.0	44.40	51.30	+15.5
5	22.96	16.07	-30.0	31.38	43.62	+39.0
6	40.56	35.20	-13.2	35.20	41.33	+17.4
7	9.95	6.89	-30.8	23.72	27.55	+16.1
Mean	20.99	15.99	-23.8	27.02	33.55	+24.2

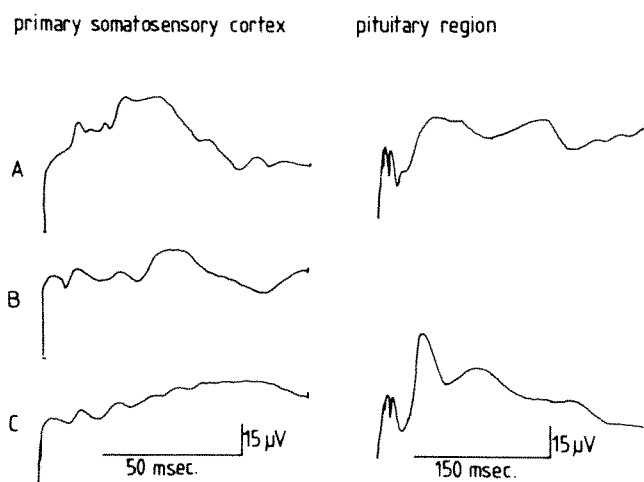


Figure 2. TPEP recordings in one of the animals. (Left) After fentanyl a decrease of the TPEP response of the primary somatosensory cortex is shown. (Right) Fentanyl-induced increase of the TPEP response in the pituitary region. (A) Control measurements. (B) 5 min after fentanyl. (C) 10 min after fentanyl.

Our present findings suggest, however, that they can also be involved as a part of sensory pathways. Thus as suggested in the past, "opiates might produce analgesia indirectly by activating a pain suppression system which in turn inhibits pain transmission" (34). Nevertheless, it is still unclear which part of the pituitary region may be involved in opiate analgesia. It might be that a part of the hypothalamic area situated near to the pituitary is involved in the mechanism. In many recorded experiments concerning the relationship between hypophysectomy and analgesia, the integrity of the hypothalamus that may be damaged by pituitary removal, has not always been verified.

Supplementary findings of our pilot studies showed that when the pituitary electrode was outside of the sella turcica, as little as 2 mm from the intended position and just touching the surface of the hypothalamic area, it was difficult to evoke responses to TPEPs in the PSC or PR. The best responses were obtained

when the electrodes were touching the stalk or the infundibular recesses, suggesting that it is this part of the pituitary that might be of importance in opiate analgesia.

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## Epidural Morphine: A Clinical Double-Blind Study of Dosage

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LANZ E, KEHRBERGER E, THEISS D. Epidural morphine: a clinical double-blind study of dosage. *Anesth Analg* 1985;64:786-91.

*The purpose of this randomized double-blind study was to determine the optimal dose of epidural morphine by establishing a dose-effect relationship. The 139 patients, who had orthopedic operations on the lower extremities, received continuous lumbar epidural anesthesia with bupivacaine, 0.75%, with or without the addition of 1, 2, 3, 4, or 5 mg of morphine hydrochloride. Analgesia and side effects were determined during the first 24 hr postoperatively. In the 12-hr period after epidural anesthesia, arterial blood gas tensions were compared between those patients who received 5 mg morphine ( $n = 13$ ) and those who received no morphine ( $n = 14$ ). Patients who received 2 or more mg of morphine were less likely to require the administration of*

*postoperative systemic analgesics ( $P < 0.05$ ). The addition of 2 or more mg of morphine to bupivacaine, 0.75%, reduced postoperative pain intensity ( $P < 0.05$ ); 5 mg of morphine reduced pain intensity for the longest time. Frequency of catheterization and pruritus increased dose-dependently. The mean  $\text{PaCO}_2$  after 5 mg of epidural morphine averaged 5 mm Hg higher than in the control group, indicating minor respiratory depression, better analgesia, or both. The dose of 3 mg of epidural morphine added to the local anesthetic is recommended for postoperative analgesia after surgery of the lower extremity; it is a compromise that provides adequate analgesia with an acceptably low frequency and intensity of side effects.*

**Key Words:** ANALGESICS—morphine. ANESTHETIC TECHNIQUE—epidural. PAIN—postoperative.

Despite the extensive use of epidural morphine for postoperative analgesia, only a few controlled double-blind studies have attempted to define the most appropriate dosage (1-5). These studies suggest that analgesia is not significantly improved when doses larger than 2-5 mg of morphine are employed.

The present study was designed to define which dose of epidural morphine is optimal in providing satisfactory postoperative analgesia with the lowest frequency and intensity of side effects (6,7). We used a randomized double-blind technique in which 0, 1, 2, 3, 4, or 5 mg of morphine were added to epidural bupivacaine given for epidural anesthesia before surgery of the lower extremity.

### Methods

After giving informed consent, 139 patients received continuous lumbar epidural anesthesia for orthopedic

surgery of the lower extremity. Prior to the study, the patients were randomly assigned to one of six groups. Epidural anesthesia consisted of bupivacaine, 0.75%, to which either 1 mg ( $n = 23$ ), 2 mg ( $n = 23$ ), 3 mg ( $n = 22$ ), 4 mg ( $n = 22$ ), or 5 mg ( $n = 25$ ) of morphine hydrochloride (Merck, Darmstadt, Germany) was added. The sixth group was the control and received no morphine. After a test dose of 4 ml bupivacaine, 0.75%, 6-16 ml bupivacaine, 0.75%, were given depending on the age, height, and weight of the patient. All patients were premedicated with 25 mg meperidine and 25 mg promethazine. During surgery, they received by choice either no systemic medication or diazepam for sedation. Only technically satisfactory procedures were included in the study.

After surgery, patients were monitored in the recovery room until the afternoon of the first postoperative day. If the patients complained of pain, they received pentazocine intramuscularly or the pyrazolone derivative dipyrone (Novalgin, Hoechst, Frankfurt, Germany) added to an intravenous sugar-electrolyte solution as analgesics. Ward personnel and the investigator were not aware of the patients' randomized groups. Postoperative data included blood pressure; heart rate; respiratory rate at hourly intervals; subjective pain rating at intervals of 2 hr for 24

Results of the study were evaluated in the doctoral dissertation of E. Kehrberger.

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Table 1. Clinical Data

	Epidural morphine dose (mg)					
	0 (n = 24)	1 (n = 23)	2 (n = 23)	3 (n = 22)	4 (n = 22)	5 (n = 25)
Age ( $\bar{x} \pm$ SD years)	51 $\pm$ 19	43 $\pm$ 22	47 $\pm$ 20	51 $\pm$ 20	46 $\pm$ 20	50 $\pm$ 20
Sex						
Female (n)	9	17	15	17	15	18
Male (n)	15	6	8	5	7	7
Height ( $\bar{x} \pm$ SD cm)	169 $\pm$ 7	166 $\pm$ 12	170 $\pm$ 10	163 $\pm$ 11	170 $\pm$ 12	163 $\pm$ 9
Weight ( $\bar{x} \pm$ SD kg)	71 $\pm$ 11	66 $\pm$ 12	70 $\pm$ 15	65 $\pm$ 12	70 $\pm$ 15	63 $\pm$ 9
Site of operation (n patients)						
Hip	12	7	8	8	10	11
Thigh	1	1	2	1	1	2
Knee	8	7	11	10	6	7
Calf	1	3	1	0	2	0
Foot	2	5	1	3	3	5
Type of operation (n patients)						
Total hip replacement	8	6	6	7	6	9
Total knee replacement	4	2	6	6	3	3
Arthrotomy	3	3	2	4	2	3
Osteotomy	2	2	1	1	2	1
Removal of metal	3	1	1	0	1	1
Other	4	9	7	4	8	8
Duration of operation ( $\bar{x} \pm$ SD hr)	2.7 $\pm$ 0.9	2.9 $\pm$ 1.3	2.8 $\pm$ 0.7	2.6 $\pm$ 0.7	2.4 $\pm$ 0.7	3.1 $\pm$ 1.2
Bupivacaine 0.75% ( $\bar{x} \pm$ SD ml)	16 $\pm$ 3	17 $\pm$ 4	17 $\pm$ 3	16 $\pm$ 3	18 $\pm$ 4	16 $\pm$ 3
Diazepam intraoperatively (n patients)	17	22	17	15	19	18
( $\bar{x} \pm$ SD mg)	9.0 $\pm$ 5.5	8.9 $\pm$ 3.2	8.8 $\pm$ 4.5	7.4 $\pm$ 3.8	9.0 $\pm$ 5.2	8.0 $\pm$ 3.6

Not significant ( $\chi^2$ -test, Kruskal-Wallis test, Mann-Whitney-Wilcoxon test).

hr after the end of surgery (1, no pain; 2, mild pain; 3, moderate pain; 4, severe pain; 5, very severe pain); time of onset of severe postoperative pain; additionally requested systemic analgesics (dose and time of administration); subjective sleep rating during the first postoperative night (good, moderate, bad); and side effects such as disturbed micturition (spontaneous or catheterization), pruritus, nausea, vomiting, fatigue, headache.

After receiving additional information and giving consent, 27 patients gave arterial blood samples obtained from a catheter placed into the radial artery. Fourteen had received bupivacaine, 0.75%, without addition of morphine, and 13 patients had received 5 mg morphine added to the local anesthetic. Gas tensions in these samples were determined with an ABL 2 (Radiometer, Copenhagen) before as well as 0.5, 1.5, 2.5, 3.5, 4.5, 6.0, 7.5, 9.0, 10.5, and 12 hr after the start of epidural anesthesia. The presence of the radial artery catheter did not identify a patient's group, as the investigator was excluded from the final decision of which groups to sample.

In addition to calculation of frequency distributions of data, statistical significance of comparisons among all groups was determined using the Kruskal-Wallis test and  $\chi^2$ -test, and between any two groups using the Mann-Whitney-Wilcoxon test and  $\chi^2$ -test. Dif-

ferences were accepted as statistically significant at an error probability of  $P < 0.05$ .

## Results

Patients in each of the six groups were similar in age, male/female ratio, body height and weight, site, type and duration of surgery, volume and dosage of bupivacaine and intraoperative sedation (Table 1), premedication (25 mg meperidine, 25 mg promethazine), and extent of epidural blockade (mean  $\pm$  SD, T8  $\pm$  2.7 segments). During the intra- and postoperative periods there were no differences among the groups with regard to ventilation as determined by respiratory rate and hemodynamics as determined by blood pressure and heart rate.

### Analgesia

Patients who received 2–5 mg epidural morphine requested additional systemic analgesics significantly less frequently than the control group within 24 hr after surgery ( $P < 0.05$ ) (Table 2). Pentazocine was administered to significantly fewer patients given 2–5 mg epidural morphine than no epidural morphine ( $P < 0.05$ ); the total doses of pentazocine were lower for the patient groups given 2–5 mg morphine than for the control group. Similarly, dipyrone was adminis-

Table 2. Supplementation\* with Systemic Analgesics and Quality of Sleep during First Postoperative Night

	Epidural morphine dose (mg)					
	0 (n = 24)	1 (n = 23)	2 (n = 23)	3 (n = 22)	4 (n = 22)	5 (n = 25)
Request for additional analgesics during 24 hr after surgery (n patients)	21	15	12 <sup>a</sup>	12 <sup>a</sup>	12 <sup>a</sup>	10 <sup>a</sup>
Pentazocine						
Administered to n patients	17	10	7 <sup>a</sup>	9 <sup>a</sup>	8 <sup>a</sup>	7 <sup>a</sup>
Total dose per group (mg)	760	540	270	390	270	240
Dipyrone						
Administered to n patients	13	9	10	6 <sup>a</sup>	5 <sup>a</sup>	6 <sup>a</sup>
Total dose per group (g)	27.5	19.0	13.4	7.0	7.4	9.4
Sleep during first postoperative night (n patients)						
Good	5	4	12 <sup>a</sup>	8	9	18 <sup>a</sup>
Moderate	7	9	4 <sup>a</sup>	8	5	2 <sup>a</sup>
Bad	12	10	7 <sup>a</sup>	6	8	5 <sup>a</sup>

\* $P < 0.05$  comparing various morphine doses with 0 mg ( $\chi^2$ -test).

tered to significantly fewer patients given 3–5 mg morphine than no epidural morphine ( $P < 0.05$ ); the total doses of dipyrone were lower for the patient group given 3–5 mg morphine than for the control group. Sleep during the first postoperative night was rated better for patients who received 2 and 5 mg morphine than for those who received no morphine ( $P < 0.05$ ).

In the control group there was almost complete analgesia for 4 hr after the start of epidural anesthesia; thereafter mean intensity of pain increased until the twelfth hr and then remained rather constant (Fig. 1). The mean intensity of pain in the group given 1 mg epidural morphine did not differ from that of the control group. After 2 mg epidural morphine, the mean intensity of pain was less than that in the control group at the twelfth hour ( $P < 0.05$ ). The epidural injection of 3 mg resulted in less pain intensity compared to that of the control group 8 ( $P = 0.05$ ), 10, and 12 hr ( $P < 0.05$ ) after injection. Four mg epidural morphine did not further decrease pain intensity, and 5 mg decreased pain intensity at the fourteenth and sixteenth hours as compared to the control group ( $P < 0.05$ ). The epidural injection of 4 mg morphine resulted in a pain course over the entire 24 hr that was almost identical to that associated with 3 mg epidural morphine. A dose of 5 mg epidural morphine resulted in a pain course that until 12 hr was very similar to that of 3 mg and thereafter was less (not statistically significant). Pain intensity at the twelfth hr was independent of age, sex, body weight, height, site, type and duration of surgery, as well as dose of bupivacaine.

### Side Effects

First postoperative micturition was delayed after 1 mg or more of epidural morphine compared to the control group ( $P < 0.05$ ) (Table 3). Spontaneous micturition

decreased linearly with increasing doses of morphine ( $P < 0.05$ ); reciprocally, the need for catheterization increased from about 12% of the patients in the control group to almost 50% of the patients receiving 5 mg morphine ( $P < 0.05$ ).

Pruritus, mainly in the face or the trunk, also increased linearly with increasing doses of morphine ( $P < 0.05$ ). It did not occur without morphine; it occurred in more than half of the patients given 4 and 5 mg ( $P < 0.05$ ). Nausea and vomiting, in most cases single occurrences of short duration, as well as headache were independent of the administration or dose of morphine.

### Blood Gases

In the control group, mean  $\text{PaCO}_2$  increased 2 mm Hg within the first 1.5 hr after administration of the local anesthetic ( $P < 0.05$ ), then gradually returned to the starting values until the sixth hr, and thereafter decreased continuously until 35 mm Hg in the twelfth hr (Fig. 2). After the epidural injection of 5 mg morphine, the mean  $\text{PaCO}_2$  increased 0.5 hr after the administration of morphine, remained significantly ( $P < 0.05$ ) elevated above starting values for 6 hr, and thereafter gradually returned to the starting values by 12 hr. From 2.5 to 12 hr, the  $\text{PaCO}_2$  values in the 5 mg morphine group averaged 5 mm Hg higher than those of the control group ( $P < 0.05$ ). The highest individual value was 57 mm Hg at 2.5 hr after epidural morphine.  $\text{PaO}_2$  and base excess were similar in both groups.

### Discussion

We administered morphine together with the local anesthetic for the following reasons: the initial epi-

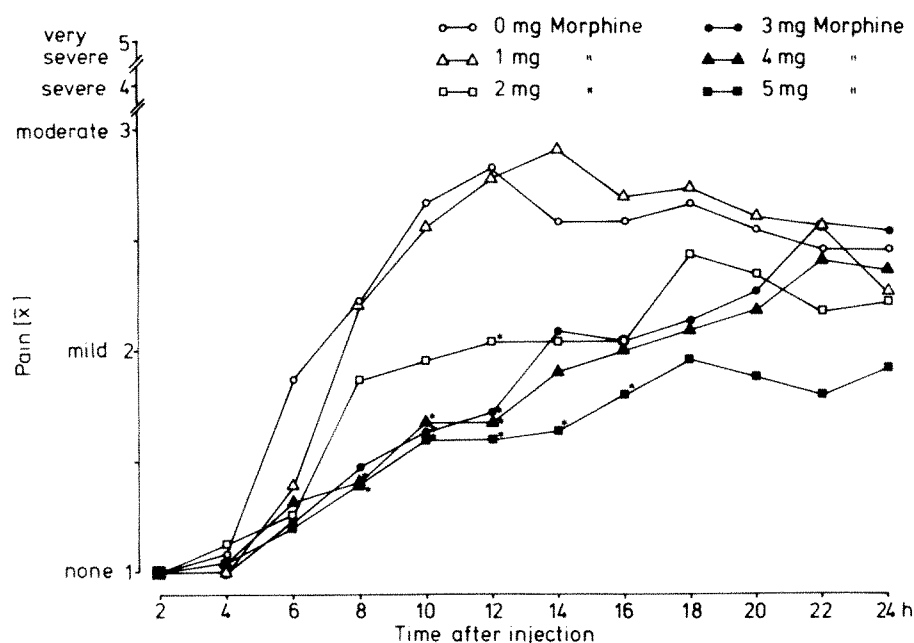


Figure 1. Mean subjective ratings of pain intensity for 24 hr after epidural anesthesia with bupivacaine, 0.75%, with 0 mg ( $n = 24$ , control group), 1 mg ( $n = 23$ ), 2 mg ( $n = 23$ ), 3 mg ( $n = 22$ ), 4 mg ( $n = 22$ ), and 5 mg ( $n = 25$ ) epidural morphine hydrochloride. For clarity the standard deviations are omitted. Symbols: \* $P < 0.05$  comparing various morphine groups with control group;  $P = 0.05$  comparing 3 mg with control group; not significant comparing 4 or 5 mg with 3 mg (Mann-Whitney-Wilcoxon test).

dural spread of morphine could be evaluated by the analgesic level of epidural anesthesia; there was no painful interval after surgery; the efficacy of epidural morphine is increased if morphine is given before the onset of pain (8); adding morphine to the local anesthetic injected epidurally permits use of a single injection epidural technique; and the combination of morphine and local anesthetic does not interfere with testing the efficacy and duration of epidural morphine because the analgesia of bupivacaine, 0.75%, completely wears off after 320 min (9) and because the duration of analgesia is the same when morphine is dissolved in either bupivacaine or saline (2).

Due to ethical reasons, our patients were not refused an analgesic when pain occurred. We administered the peripherally acting pyrazolone derivative dipyrone or the centrally acting opioid pentazocine. Like other investigators (10), we used pentazocine, an agonist-antagonist, which reverses possible respiratory depression induced by morphine (11) without reversing the analgesic effect of morphine, an effect also observed after naloxone (12).

Due to supplementation with systemic analgesics, we were not able to quantitate the analgesic effect of epidural morphine alone. Patients who received 0–1 mg morphine were more likely to require systemic analgesics than those who received higher doses of morphine, consequently diminishing the differences in pain intensity between these groups. If we had not used supplementary analgesics, these differences would have become more marked.

Our methods of measuring postoperative analgesia were of different reliability. The supplementation with

systemic analgesics not only reflects pain intensity but also the attitude of patients and nursing personnel towards pain and its therapy with analgesics. We preferred the pain assessment made by the patient him or herself rather than observer assessment, as the former is more reliable (13). The simple 5-graded verbal scale of pain intensity correlates well with the visual analogue pain scale (14). Pain is only one of many factors determining sleep quality during the first postoperative night.

Our results show the following relationships between epidural morphine dose and postoperative analgesia: when 2–3 mg and more morphine was administered, fewer patients required systemic analgesics. Postoperative pain intensity was significantly less with 2 mg epidural morphine than it was when no epidural morphine was given. The decrease in pain intensity was even more marked and longer after 3 mg than after 2 mg, and lasted still longer after 5 mg.

Two side effects showed a linear relationship with the dose of epidural morphine: catheterization and pruritus. The need for catheterization was more frequent by patients who received 5 mg morphine than by those in the control group ( $P < 0.05$ ), and the occurrence of pruritus was more frequent in those who received 3 mg ( $P < 0.05$ ). The first spontaneous micturition was delayed after doses of 1 mg and more of morphine. After doses of up to 5 mg epidural morphine, nausea and vomiting were no more frequent than they were when no morphine was given. These side effects appear to be more frequent after doses of 8 mg (3) and 10 mg (6).

None of our patients had obvious clinical signs of

Table 3. Side Effects

	Epidural morphine dose (mg)					
	0 (n = 24)	1 (n = 23)	2 (n = 23)	3 (n = 22)	4 (n = 22)	5 (n = 25)
Disturbances of micturition						
1st micturition ( $\bar{x} \pm$ SD hr after epidural anesthesia)	9.8 $\pm$ 2.7	13.3 $\pm$ 3.2 <sup>a</sup>	13.0 $\pm$ 3.5 <sup>a</sup>	13.8 $\pm$ 3.6 <sup>a</sup>	14.0 $\pm$ 4.4 <sup>a</sup>	13.5 $\pm$ 3.9 <sup>a</sup>
Spontaneous micturition <sup>c</sup> (n patients)	21	18	16	15	17	13 <sup>b</sup>
Catheterization <sup>c</sup> (n)	3	5	7	7	5	12 <sup>b</sup>
Pruritus <sup>c</sup> (n)	0	4	5	7 <sup>b</sup>	13 <sup>b</sup>	14 <sup>b</sup>
Nausea (n)	7	8	8	10	6	8
Vomiting (n)	5	4	6	6	3	6
Headache (n)	5	2	5	1	4	4

<sup>a</sup> $P < 0.05$  comparing 1–5 mg morphine with 0 mg (Mann–Whitney–Wilcoxon test).<sup>b</sup> $P < 0.05$  comparing 3, 4, and 5 mg with 0 mg ( $\chi^2$ -test).<sup>c</sup>Linear regression: for spontaneous micturition  $r = 0.975$ ,  $P < 0.005$ ; for catheterization  $r = 0.802$ ,  $P < 0.025$ ; for pruritus  $r = 0.965$ ,  $P < 0.001$  ( $2 \times K$  table for trend).

respiratory depression for 24 hr after epidural morphine. We examined the  $\text{PaCO}_2$  values only in the control group and in the group receiving our study's highest dose of 5 mg, because the greatest differences were expected here. We measured  $\text{PaCO}_2$  for only the first 12 hr to avoid any possible complications that might be associated with leaving the arterial cannula in place for 24 hr. The mean  $\text{PaCO}_2$  after epidural morphine was 5 mm Hg above the values of the control group from the second hr until the end of measurements at 12 hr. This finding can be ascribed, at least during the time of complete analgesia from the local anesthetic, to respiratory depression associated with the anesthetic technique. After the epidural anesthesia had worn off, the higher  $\text{PaCO}_2$  values associated with epidural morphine may be explained either by respiratory depression, better analgesia, or both. It is questionable whether the respiratory depression we observed is dangerous, as it is in the range of  $\text{PaCO}_2$  observed during physiologic sleep (15). However, respiratory depression may become a risk with additional and repeated systemic administration of opiates and sedatives, especially in older patients and when using thoracic epidural narcotics (16). Our study gave no evidence of delayed respiratory depression.

The relationships between morphine dose and analgesia on the one hand and side effects on the other hand suggest that the optimal dose of epidural morphine for surgery of the lower extremities is 3 mg for the following reasons. First, the need for systemic supplementation and the time of its administration were comparable for 3- and 5-mg doses. Also, although 5 mg produced longer duration of analgesia, the intensity of postoperative pain after 12 hr was not significantly different between the 3-mg and the 5-

mg dose of epidural morphine. The curves of pain intensity after the different doses of morphine indicate that doses greater than 3 mg do not appreciably improve postoperative analgesia, a ceiling effect perhaps explained by rather complete occupation of the opiate receptors by morphine with 3-mg doses. Second, the side effects, urinary retention with the need for catheterization as well as pruritus, were dose-dependent. The frequency of catheterization decreased from 48 to 32% when the dose was decreased from 5 to 3 mg epidural morphine. Finally, the increased  $\text{PaCO}_2$  values with 5 mg epidural morphine and the reported dose-dependent respiratory depression after epidural morphine (17) also suggest that a dose reduction to 3 mg may be associated with greater patient safety.

Our recommendation of 3 mg morphine corresponds well with the results of other investigators who compared postoperative analgesia after surgery of the lower extremities after different doses of morphine and who found no differences in analgesia between 2 and 4 mg (2); among 2, 4, and 8 mg (3); or between 3 and 5 mg (4) of epidural morphine. The analgesia produced by epidural morphine is, however, less complete than that associated with epidural local anesthetics. The former does not always offer complete analgesia but almost always markedly reduces postoperative pain. The common experience with epidural opiate analgesia also indicates a marked variability of intensity and duration of analgesia; incomplete analgesia may be encountered even after high doses, which cannot be recommended due to their higher rates of complications.

The dose of 3 mg epidural morphine appears to us an optimal compromise for postoperative analgesia after surgery of the lower extremities. This dose offers



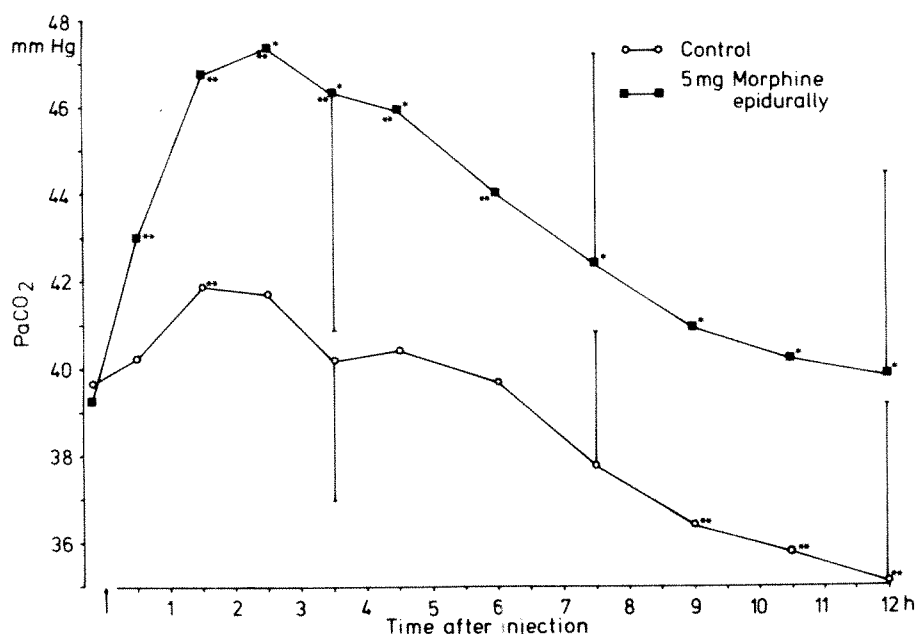


Figure 2. Mean  $\pm$  SD  $\text{PaCO}_2$  for 12 hr after epidural anesthesia with bupivacaine, 0.75%, with 0 mg ( $n = 14$ ) and with 5 mg epidural morphine ( $n = 13$ ). For clarity only a few standard deviations are presented. Symbols: \*\* $P < 0.05$  comparing the values of a group with its starting values (Mann-Whitney-Wilcoxon test); \* $P < 0.05$  comparing the values of the morphine group with those of the control group (Mann-Whitney-Wilcoxon test);  $\uparrow$ , start of epidural anesthesia.

sufficient analgesia; increasing the dose intensifies analgesia slightly and prolongs duration of analgesia but also increases the dose-dependent side effects such as urinary retention, pruritus, and respiratory depression.

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## Anesthesia for Termination of Pregnancy: Midazolam Compared with Methohexital

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VERMA R, RAMASUBRAMANIAN R, SACHAR RM.  
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*Clinical effects of intermittent intravenous administration of midazolam were compared with those of methohexital in two groups of ten premedicated patients each undergoing suction termination of pregnancy under general anesthesia. Both groups received intravenous fentanyl (1 µg/kg) 5 min*

*prior to administration of the induction agent. No significant difference was found between the two groups in induction time and quality of anesthesia. The recovery time was significantly (17 min) longer in patients who received midazolam ( $P < 0.0001$ ).*

**Key Words:** HYPNOTICS, BENZODIAZEPINES—midazolam. HYPNOTICS, BARBITUATES—methohexital. ANESTHESIA, INTRAVENOUS—midazolam, methohexital.

Termination of pregnancy in the first fourteen weeks of gestation by suction under general anesthesia is common in ambulatory gynecological surgery. Anesthesia for this procedure is not without risks (1). Ideally the technique should include rapid, smooth induction and maintenance of an appropriate level of anesthesia without increasing blood loss or provoking cardiorespiratory instability. The recovery should be fast; and complications, such as nausea, vomiting, and anaphylactoid reactions, should be absent.

Both inhalational and intravenous techniques have been advocated for this procedure (2,3). Studies of intravenous anesthetic techniques for short surgical procedures have compared midazolam with thiopental (3,4). Although thiopental is still considered the "gold standard" of comparison for induction agents (4), it possesses many adverse characteristics, including a cumulative effect, possible liver dysfunction on repeated injection, and slow elimination (5) (half-life is 5–12 hr). These features render its use for intermittent intravenous anesthesia for short surgical procedures undesirable.

Methohexital, a methyl barbiturate, introduced into clinical anesthesia by Stoelting (6), is more rapidly metabolized and has a relatively short elimination half-

life of 75–125 min. Its use has been advocated where rapid recovery of consciousness and early ambulation are desired (7).

Midazolam, a short-acting water soluble benzodiazepine, is finding increasing use in anesthesia for patients undergoing various types of outpatient surgical procedures. Its short duration of action, rapid elimination, and relative lack of side effects make it a particularly attractive choice.

The following study was undertaken to compare the clinical effects of midazolam with methohexital when these agents were administered intravenously by intermittent injection in outpatients undergoing suction termination of pregnancy.

### Methods

The study was reviewed and approved by the ethical committee of the hospital. Twenty healthy women (ASA physical status I or II; age 18–28 yr) undergoing elective suction termination of pregnancy (gestation 8–14 weeks) were randomly assigned to one of two groups to receive midazolam (group A) or methohexital (group B). Both groups were premedicated with intramuscular papaveretum (omnopon) (10 mg) and scopolamine (0.2 mg) administered 1 hr before operation. Blood pressure, heart rate, and respiratory rate were recorded prior to and after administration of the drugs at 5-min intervals. Both groups received fentanyl (1 µg/kg) 5 min prior to induction of anesthesia via an 18-gauge intravenous plastic cannula

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placed in a superficial vein on the dorsum of the hand. Anesthesia was induced intravenously with either midazolam (0.15 mg/kg) (group A) or methohexital (1 mg/kg) (group B) over 10–15 sec. The induction was considered complete when the eyelash reflex was lost, after which anesthesia was maintained with 66% nitrous oxide in oxygen administered through a Maggill's circuit. The induction time was defined as the time between the completion of the administration of the intravenous anesthetic agent and the loss of eyelash reflex. Increments of either midazolam (2.5 mg) or methohexital (10 mg) were given during the procedure if signs of inadequate anesthesia such as movements, lacrimation, sweating, changes in blood pressure or heart rate were noticed. Complications, such as pain on injection, cough, hiccup, apnea, laryngospasm, bronchospasm, rashes, hypotension, and nausea or vomiting during induction, maintenance, and recovery were recorded. The overall quality of anesthesia was graded by the anesthesiologist on a three point scale: good = 1; satisfactory = 2; and poor = 3. The induction dose, induction time, duration of anesthesia (defined as the time between the loss of eyelash reflex and the discontinuation of nitrous oxide), and the number of increments of the hypnotic agent given were also recorded. The interval between discontinuation of nitrous oxide and the time when the patient responded purposefully to oral commands was recorded as the recovery time.

Student's *t*-test was utilized to analyze the data for statistical significance and results were considered significant at  $P < 0.05$ . Results are given as means  $\pm$  standard deviations.

## Results

The main findings of the study are summarized in Table 1. No statistically significant difference between the two groups was found in terms of patients' weights, dose of fentanyl administered, induction time, or duration of anesthesia. The mean induction time in the group receiving midazolam (group A) was  $36.7 \pm 15.2$  sec, and in the group receiving methohexital (group B) was  $41 \pm 34.5$  sec. This difference was not statistically significant ( $P = 0.937$ ). The group receiving midazolam (group A) received an induction dose of  $8.8 \pm 1.5$  mg and a total dose of  $17.8 \pm 3.8$  mg. The group receiving methohexital (group B) received an induction dose of  $58.5 \pm 9.1$  mg and a total dose of  $127.5 \pm 22.8$  mg. Recovery, as defined above, occurred in  $20.1 \pm 8.4$  min in the group receiving midazolam (group A) and in  $3.2 \pm 2.4$  min in the group receiving methohexital (group B); this difference being statistically highly significant ( $P < 0.0001$ ).

Table 1.

	Group A (midazolam) <i>n</i> = 10 Mean (SD)	Group B (methohexital) <i>n</i> = 10 Mean (SD)
Weight (kg)	58.8 (10.3)	58.5 (9.1)
Induction time (sec)	36 (15.2)	41 (34.5)
Duration of anesthesia (min)	11.7 (3.3)	13 (4.5)
Number of incremental doses	3.6 (1.3)	6.9 (2.2)
Assessment score	1.8 (0.42)	1.7 (0.48)
Total dose	17.8 (3.8)	127.5 (22.8)
Recovery time (min)	20.1 (8.4) <sup>a</sup>	3.2 (2.4) <sup>a</sup>

Mean and standard deviation values of observations between group A (midazolam) and group B (methohexital).

<sup>a</sup> $P < 0.0001$

No serious cardiorespiratory complications were noted during the study. Even though patients in the group receiving methohexital required a greater number of incremental doses for maintenance of anesthesia, the mean scores for the overall quality of anesthesia were not significantly different in the two groups. Two patients in the group receiving methohexital experienced pain on injection and one patient in each group exhibited a mild rash after the administration of the induction agent.

## Discussion

Therapeutic abortion during the first trimester of pregnancy can be performed under regional or general anesthesia. Both intravenous and inhalational anesthetic techniques have their proponents. The use of rapid-acting intravenous anesthetics is finding a prominent place in contemporary outpatient anesthesia practice. These agents may be administered by intermittent injection or by continuous intravenous infusion. In our busy unit, which has a fast turnover of patients, practical considerations such as ease of administration, simplicity, type of equipment required, and the relatively short duration of the gynecological procedure involved influenced our preference for intermittent injection.

An ideal intravenous anesthetic agent for outpatient anesthesia should have a fast onset and short duration of action. It should be rapidly metabolized into pharmacologically inactive and nontoxic metabolites. There should be no cumulation after repeated doses. Cardiorespiratory stability, good local tissue tolerance, and lack of allergic phenomena should be assured. Midazolam fulfills some of these criteria. It is relatively fast-acting and is biotransformed in the liver into inactive metabolites. The elimination half-life is 90–160 min (8,9) and, in common with other benzodiazepines, is virtually devoid of allergic reac-

tions. The induction dose of 0.15 mg/kg was chosen on the basis of experience of other investigators (10,11) and ourselves of using midazolam as an induction agent in patients premedicated with narcotics. It also reflects our desire to achieve smooth and successful induction of general anesthesia with a minimal amount of the induction agent—one of the cardinal principles of outpatient anesthesia. Similar experience and considerations influenced our choice of the induction dose of methohexital.

Our study shows that midazolam compares favorably with methohexital in terms of induction characteristics and the overall quality of anesthesia. The mean induction time of 36.1 sec for midazolam is considerably shorter than that reported in two studies by Reves et al. (4,12) (73 and 107 sec  $\pm$  SEM of 8.9 and 19.1 sec, respectively) and by Fragen et al. (13) (mean 175 sec). This is probably related to premedication and administration of intravenous fentanyl 5 min prior to induction of anesthesia in our patients.

Recovery from unconsciousness and narcotic effects, and the ultimate regaining of all cognitive functions may be assessed in several different ways. Many tests of recovery that have been proposed in the past illustrate this point. They vary in complexity and sensitivity. To be of any clinical value, however, they should be simple, sensitive, easy to perform, and not time consuming. We assessed recovery in terms of overall ability of our patients to respond purposefully to oral commands and answer questions that were designed to test their orientation in time and space. Our study shows that midazolam, when administered by intermittent intravenous injections to maintain anesthesia, results in recovery time that is significantly longer (by 17 min) than that after similar use of methohexital. Although the relatively prolonged recovery time does not preclude the use of midazolam

for short surgical procedures, it may be of importance in busy units with limited recovery facilities and a rapid turnover of patients.

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## Induction Dose-Response Curves for Midazolam and Ketamine in Premedicated ASA Class III and IV Patients

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GROSS JB, CALDWELL CB, EDWARDS MW. Induction dose-response curves for midazolam and ketamine in premedicated ASA class III and IV patients. *Anesth Analg* 1985;64:795-800.

Using probit analysis, dose-response curves for induction of anesthesia with midazolam or ketamine were constructed in ASA class III and IV patients premedicated with morphine, 0.1 mg/kg, and glycopyrrolate, 4  $\mu$ g/kg. For ketamine,  $ED_{50}$  values for abolition of the response to verbal commands, eyelash stimulation, and painful stimulation were 0.9, 1.3, and 1.3 mg/kg, respectively; corresponding  $ED_{95}$  values were 1.6, 2.3, and 4.3 mg/kg, which are within the range of clinically recommended doses. For midazolam,  $ED_{50}$  values for verbal commands, eyelash stimulation, and painful stimulation were 0.19, 0.24, and 0.36 mg/kg, significantly greater than those previously reported for unpremedicated ASA class I and II patients. The corresponding  $ED_{95}$  values, 0.35, 0.43, and 1.04 mg/kg exceed previously

reported values and are appreciably greater than the doses used in most previous studies of midazolam induction.

Midazolam decreased systolic blood pressure slightly but significantly (from  $138 \pm 4$  to  $128 \pm 4$  mm Hg,  $\bar{X} \pm SEM$ ,  $P < 0.005$ ), while diastolic blood pressure and heart rate remained unchanged. In contrast, ketamine increased systolic blood pressure (from  $141 \pm 4$  to  $164 \pm 5$  mm Hg,  $P < 0.005$ ), diastolic blood pressure (from  $71 \pm 3$  to  $88 \pm 4$  mm Hg,  $P < 0.005$ ), and heart rate (from  $84 \pm 2$  to  $102 \pm 4$  beats/min,  $P < 0.005$ ). On the basis of these data, we conclude that in ASA class III and IV patients, midazolam induction allows for hemodynamic stability and avoids the significant tachycardia and hypertension associated with equipotent doses of ketamine.

**Key Words:** INDUCTION, ANESTHESIA—midazolam, ketamine.

Because it maintains hemodynamic stability and induces anesthesia smoothly, midazolam is a potential alternative to barbiturates or ketamine for induction of anesthesia in high-risk patients. In premedicated ASA physical status III and IV patients, induction of anesthesia with midazolam, 0.15–0.3 mg/kg, maintains cardiac output and decreases peripheral vascular resistance and mean arterial pressure by approximately 15% (1–4). The dose variation in these studies reflects the absence of adequate dose-response data for midazolam induction in such patients. Reves (5,6) reported that in unpremedicated patients, midazolam's  $ED_{50}$  for abolition of the response to verbal commands and eyelash stimulation was 0.13 mg/kg, with a corresponding  $ED_{95}$  of 0.20 mg/kg. In contrast, we

found, in an earlier study, that midazolam, 0.2 mg/kg, abolished the response to verbal commands and eyelash stimulation in only 43% of unpremedicated subjects (7). Berggren and Eriksson (8) found that in healthy patients premedicated with diazepam and meperidine, the mean dose of midazolam required to abolish the eyelid reflex was 0.36 mg/kg. In view of the uncertainties regarding the appropriate induction dose of midazolam, we designed the present study to determine the dose-response curves for abolition of responses to verbal commands, eyelash stimulation, and painful stimulation in ASA class III and IV patients premedicated with morphine. For comparison, we also evaluated ketamine, another agent useful for induction of anesthesia in high-risk patients.

### Methods

Fifty-seven male patients, ASA class III and IV, scheduled for elective surgery, consented to participate in this study, which was approved by our institutional review boards. We excluded patients with hypertension, coronary artery disease, intracranial mass lesions, or other contraindications to ketamine or mid-

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azolam. Subjects fasted for at least 8 hr, and had not taken benzodiazepines or ethanol for a minimum of five days before the study. One hour ( $\pm 15$  min) before induction of anesthesia, subjects received morphine sulfate, 0.1 mg/kg, and glycopyrrolate, 4  $\mu$ g/kg intramuscularly. We then established ECG and blood pressure (oscillotonometer) monitoring (9), and started two intravenous infusions: the first, a 20-gauge Teflon catheter flushed with 0.9% NaCl for administration of the induction agent only, the other for perioperative administration of fluids and other medications.

For one min before induction, subjects breathed oxygen while one investigator recorded baseline blood pressure (BP) and heart rate (HR) values. A second investigator then injected a predetermined dose of either midazolam or ketamine (see below) over 15 sec. The first investigator, unaware of which drug had been injected, continually assessed subjects' levels of consciousness and recorded the times from the start of injection until disappearance of the eyelash reflex, the ability to respond to the command "open your eyes," and purposeful response to pinching the trapezius muscle. He also recorded vital signs at 1-min intervals. If all three responses were not abolished within 2 min from the start of drug injection, subjects received additional doses of midazolam (0.05 mg/kg) or ketamine (0.5 mg/kg) at 2-min intervals until induction was complete. Patients who remained responsive after three incremental doses of midazolam or ketamine received thiopental, 1–2 mg/kg, to complete induction. Immediately after induction was accomplished, we recorded BP and HR and then deepened anesthesia as necessary, either with inhaled or intravenous anesthetics. Postoperatively, we recorded the times from the end of surgery until patients became responsive to verbal commands and the times until patients were fit for discharge from the recovery room. One and seven days after surgery, an observer, who was unaware of which drug had been injected, examined the patient for evidence of venous irritation (tenderness, erythema, or induration) at the injection site.

We randomized subjects to receive midazolam or ketamine in blocks of six, enabling us to assess and, if necessary, adjust the initial dose of each drug at six-subject intervals. For the first six subjects, the initial dose of midazolam was 0.15 mg/kg, and that of ketamine was 1.0 mg/kg. If more than one subject who received a given initial dose of midazolam or ketamine required supplemental doses to complete induction, we increased the initial dose of midazolam (by 0.05 mg/kg) or ketamine (by 0.5 mg/kg) for the next block of six subjects. After finding doses of midazolam and ketamine that reliably induced anesthesia

Table 1. Underlying Medical Problems

	Midazolam	Ketamine
Peripheral vascular disease	7	9
Chronic obstructive pulmonary disease	7	3
Metastatic tumor	5	6
Diabetes	4	3
Congestive heart failure	2	0
Pancreatitis	1	0
Multiple sclerosis	1	1
Collagen vascular disease	1	1
Glomerulonephritis	1	0
Cachexia	1	0
Sepsis	0	1
Renal failure	0	1
Hemorrhage	0	1
Jaundice	0	1
Total	30	27

in at least two of three patients, we randomized an additional 24 patients to receive this dose of midazolam or ketamine for hemodynamic evaluation.

Our 2-min dosing interval was short compared with the redistribution half-lives of midazolam (7.2 min) (10) and ketamine (17.6 min) (11). This allowed us to use cumulative drug doses (12) in the log-probit analysis (13) that determined the ED<sub>50</sub> and ED<sub>95</sub> for each endpoint (abolition of eyelash reflex, response to commands, and response to painful stimulation). After excluding subjects who received thiopental to supplement induction, we used two-way analysis of variance to determine the statistical significance of changes in systolic and diastolic blood pressures, as well as heart rate accompanying induction of anesthesia with each drug. One-way analysis of variance compared changes in hemodynamic variables after midazolam with those after ketamine. Fisher's exact test determined the significance of differences in the incidence of venous irritation and dysphoria between the two drugs.  $P < 0.05$  indicated statistical significance.

## Results

Thirty patients received midazolam (cumulative doses of 0.15–0.50 mg/kg), and 27 patients received ketamine (cumulative doses of 1.0–3.0 mg/kg). Ages and weights of the midazolam recipients ( $60 \pm 2$  yr,  $69 \pm 2$  kg,  $\bar{X} \pm \text{SEM}$ ) did not differ significantly from those of the ketamine recipients ( $59 \pm 1$  yr,  $72 \pm 3$  kg). Tables 1 and 2 indicate the underlying medical problems and surgical procedures performed on patients in whom anesthesia was induced with midazolam or ketamine. Seven patients required supplemental thiopental after cumulative midazolam doses

Table 2. Surgical Procedures

	Midazolam	Ketamine
Peripheral surgery	9	5
Laparotomy	5	10
Urologic surgery	5	2
Oral surgery	5	0
Otorhinolaryngologic surgery	3	0
Thoracotomy	1	4
Orthopedic surgery	1	3
Vascular reconstruction	1	3
Total	30	27

of 0.30–0.50 mg/kg; only one patient required supplemental thiopental after ketamine, 2.5 mg/kg.

For midazolam, the  $ED_{50}$  values for abolition of the response to verbal commands, eyelash reflex, and trapezius squeeze were 0.19, 0.24, and 0.36 mg/kg, respectively; corresponding  $ED_{95}$  values were 0.35, 0.43, and 1.04 mg/kg (Fig. 1). For ketamine,  $ED_{50}$  values for verbal commands, eyelash reflex, and trapezius squeeze were 0.9, 1.3, and 1.3 mg/kg; corresponding  $ED_{95}$  values were 1.6, 2.3, and 4.3 mg/kg (Fig. 2).

Midazolam induction (without supplemental thiopental,  $n = 23$ ) decreased systolic blood pressure from  $138 \pm 4$  to  $128 \pm 4$  mm Hg ( $\bar{X} \pm SEM$ ,  $P < 0.005$ ), diastolic blood pressure remained unchanged at  $71 \pm 2$  mm Hg, and heart rate increased insignificantly (from  $85 \pm 4$  to  $88 \pm 3$  beats/min). Ketamine induction ( $n = 26$ ) increased systolic blood pressure (from  $141 \pm 4$  to  $164 \pm 5$  mm Hg,  $P < 0.005$ ), diastolic blood pressure (from  $71 \pm 3$  to  $88 \pm 4$  mm Hg,  $P < 0.005$ ), and heart rate (from  $84 \pm 2$  to  $102 \pm 4$  beats/min,  $P < 0.005$ ). Heart rate increased significantly more after ketamine than after midazolam ( $P < 0.05$ ). The increased systolic and diastolic blood pressures after ketamine differ significantly from the decreased systolic and unchanged diastolic blood pressure after midazolam ( $P < 0.001$ ). Nineteen of the 27 patients in whom anesthesia was induced with ketamine received no supplemental intravenous anesthetics; maintenance was solely with nitrous oxide and halothane, enflurane, or isoflurane. In this subgroup of patients, the time from discontinuation of inhalational anesthetics until patients responded to commands was  $12 \pm 5$  min; the time from discontinuation of anesthesia until patients were fit for discharge from the postanesthesia room was  $106 \pm 11$  min. Twenty-six of the thirty patients given midazolam received no supplemental intravenous agents; in these patients, times for response to commands ( $24 \pm 5$  min) and discharge from the postanesthesia room ( $141 \pm 17$  min) did not differ significantly from those of the ketamine patients.

Four of the 27 patients receiving ketamine reported dysphoria related to anesthesia; none of the 30 patients receiving midazolam had such a reaction ( $P < 0.05$ ). The incidence of venous irritation did not differ significantly between midazolam (7%) and ketamine (22%). There was no persistent venous thrombosis, and all instances of phlebitis were successfully managed with conservative therapy (warm soaks and non-narcotic analgesics).

## Discussion

Until now, the only available dose–response data for midazolam have been those obtained in unpremedicated healthy patients as reported by Reves et al. (5,6). However, the following inconsistencies make their data difficult to interpret. First, midazolam, 0.2 mg/kg, abolished the response to verbal commands and eyelash stimulation in all of their patients. Because this corresponds to an infinite probit, data for this dose could not be included in the analysis (14). Therefore, their log–dose vs probit regression line had only two defined points and zero degrees of freedom, making it impossible to determine its confidence limits.

Second, in several other studies, midazolam doses in excess of 0.2 mg/kg (Reves'  $ED_{95}$ ) failed to abolish the eyelash reflex and response to verbal commands in a significant fraction of patients. For example, Kanto et al. (15) found that a minimum of 0.3 mg/kg midazolam was necessary for induction of anesthesia in healthy patients premedicated with narcotics. In fact, three such patients who received midazolam, 0.45 mg/kg, required supplemental thiopental, 0.9 mg/kg, to complete induction. Kanto's experimental design did not allow determination of the dose–response relationship for midazolam: the endpoint for induction was not clearly defined, and the number of successful and unsuccessful inductions at each dose level was not clearly presented (the authors emphasized the time required for induction rather than the efficacy of a given induction dose). Berggren and Eriksson (8) found that 0.36 mg/kg was the mean midazolam dose necessary to abolish the eyelash reflex in ASA I patients premedicated with diazepam and meperidine. However, they did not evaluate other responses or obtain dose–response data.

Despite the fact that our patients received narcotic premedication,  $ED_{50}$  values for abolition of the response to verbal commands (0.19 mg/kg) and eyelash stimulation (0.24 mg/kg) were significantly greater than those reported by Reves (0.13 mg/kg for abolition of both responses) (5,6). These differences are especially surprising because our patients had significant systemic disease and would therefore be expected to re-

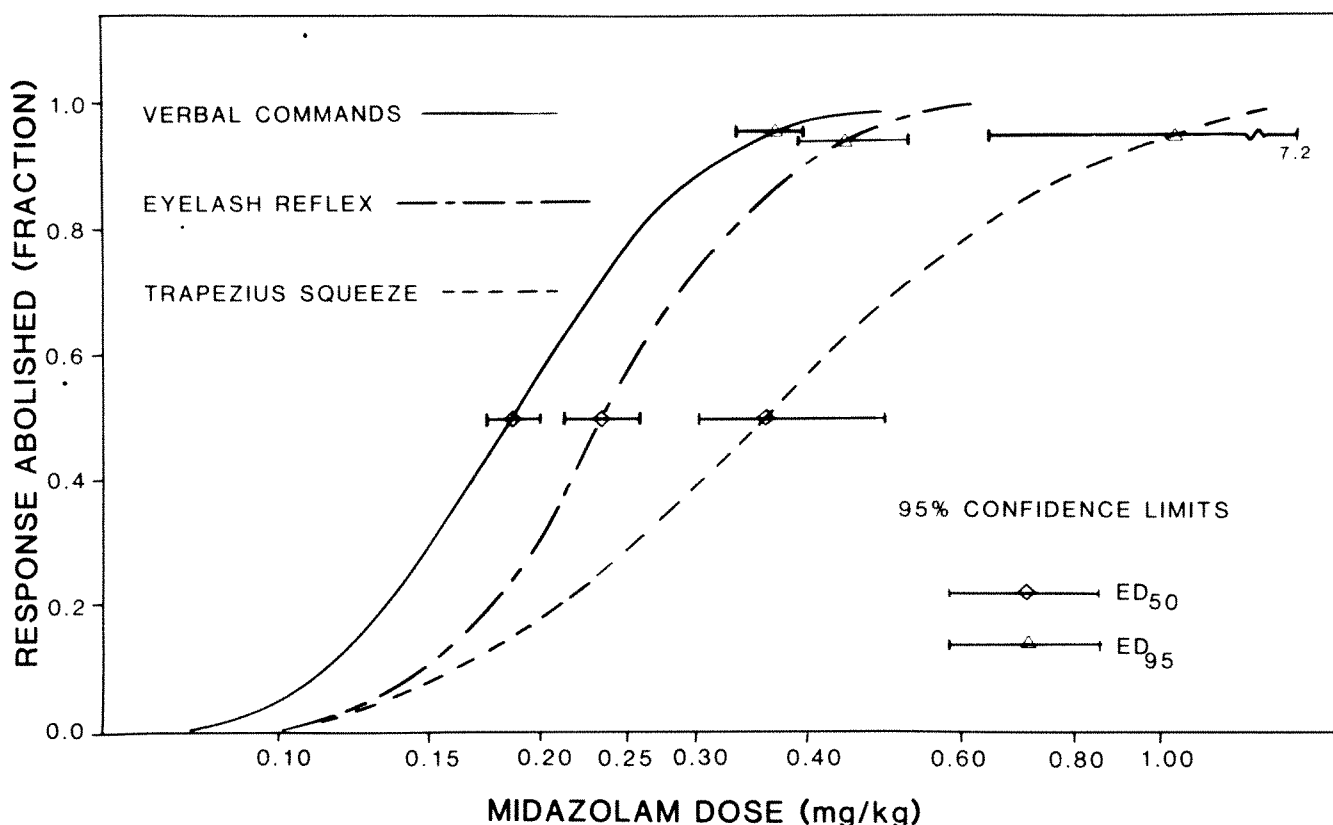


Figure 1. Cumulative midazolam dose (log scale) vs response curves for abolition of reaction to verbal commands, eyelash stimulation, and painful stimulation (trapezius squeeze).

quire smaller doses of anesthetics. Of course, the ED<sub>50</sub> abolishes a given response in only half of the subjects; the other half continue to respond. ED<sub>95</sub> is a better indicator of an effective induction dose (6,16). Our ED<sub>95</sub> values (0.35 mg/kg for verbal commands, 0.43 mg/kg for eyelash response) are similar to the doses used by Berggren and Kanto but far in excess of the 0.2 mg/kg reported by Reves.

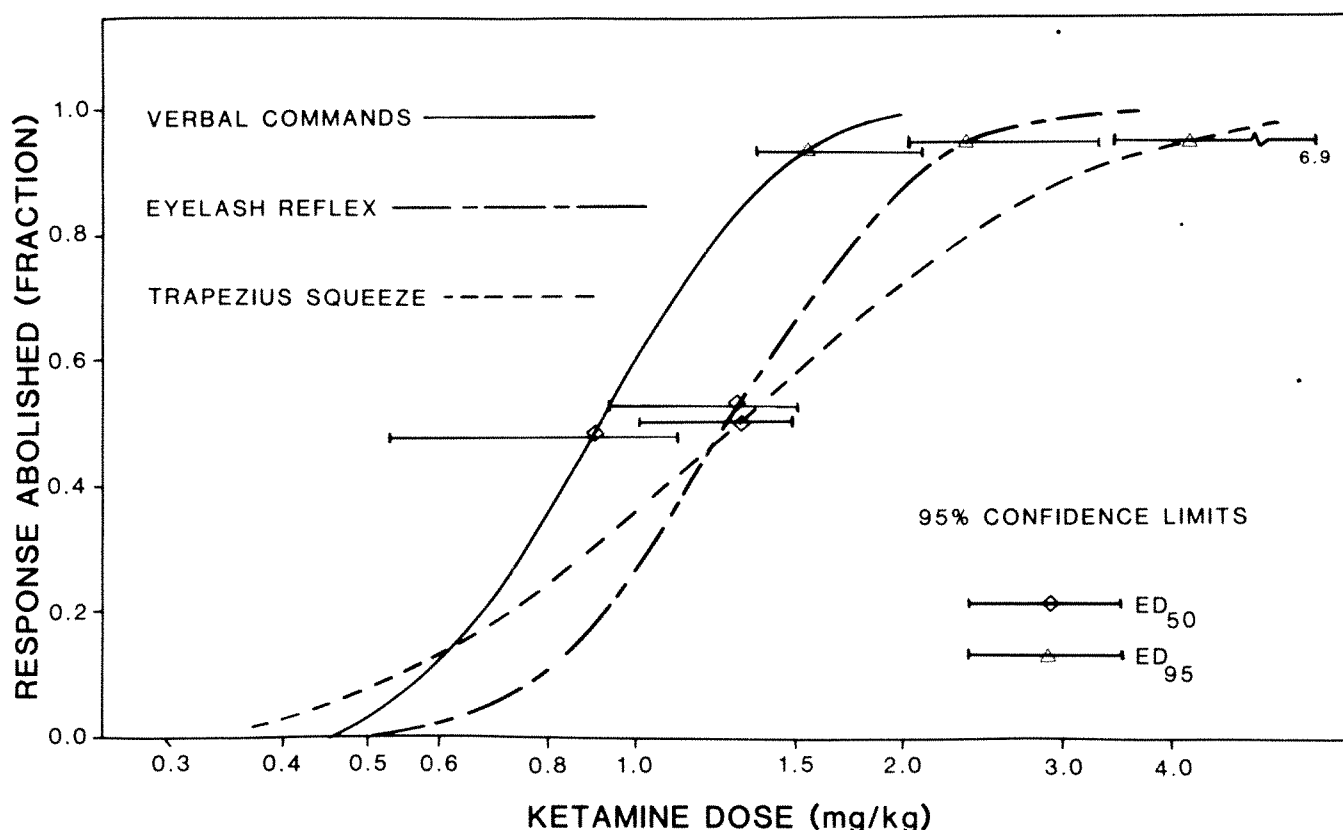
None of the previous investigators attempted to determine whether a given dose of midazolam abolished movement in response to painful stimulation (analogous to the MAC of an inhaled agent) (17). In some previous midazolam induction studies, inhalation anesthetics (2,8,15,18,19) or muscle relaxants (2,18-20) were administered before laryngoscopy or surgical incision, and in others (1,3,4,6,21,22), timing of the administration of additional agents was not specified. The present data suggest that if midazolam is used as the sole anesthetic before painful stimulation, large doses may be necessary. The ED<sub>50</sub> to abolish the response to painful stimulation in our morphine-premedicated patients was 0.36 mg/kg; the

ED<sub>95</sub> was 1.04 mg/kg, more than double the highest previously reported "induction dose." (The broad confidence limits for this value suggest that midazolam is a relatively ineffective analgesic.) However, because the hemodynamic effects of midazolam doses approaching 1 mg/kg are not known in humans, we cannot recommend their use. As an alternative, we found that an initial midazolam dose of 0.35 mg/kg followed, if necessary, by up to three incremental doses of 0.05 mg/kg completely induced anesthesia in 14 of 15 patients (the remaining patient required thiopental, 2 mg/kg, to complete induction).

Lebowitz et al. (3) documented the minimal hemodynamic effects of midazolam, 0.15 mg/kg, in ASA class III patients without cardiac disease. Although our patients received significantly larger doses of midazolam ( $0.34 \pm 0.01$  mg/kg) than did those of Lebowitz et al., the cardiovascular effects were similar: a slight but statistically significant decrease in blood pressure with no significant change in heart rate. Therefore, although induction of anesthesia may require larger doses of midazolam than previously thought necessary, midazolam doses as large as 0.35 mg/kg can safely be used to induce anesthesia in ASA class III and IV patients.

We previously reported that some patients tend to be slow to awaken after midazolam induction (23).





However, the present data do not justify the conclusion that midazolam induction delays emergence from anesthesia. Although we analyzed recovery data only for patients who received no supplemental intravenous anesthetics, our inability to document a difference between midazolam- and ketamine-induced patients may be related to the intragroup variability resulting from nonstandardized maintenance regimens, surgical procedures, and duration of anesthesia.

Previous dose-response data for ketamine are also incomplete. Wulfsohn (24) reported that ketamine, 1.9 mg/kg of lean body mass (1.3 mg/kg of total body weight) reliably induced strabismus and nystagmus in minimally premedicated healthy patients. However, this dose abolished the eyelash reflex in only 1 of 22 patients. It is not surprising, therefore, that we found a slightly higher  $ED_{95}$  for abolition of the eyelash response: 2.3 mg/kg. Because there may have been instances when involuntary movements associated with ketamine injection were misinterpreted as purposeful movements in response to painful stimulation, we may have overestimated the  $ED_{95}$  for abolition of this response. Nonetheless, our value of 4.3 mg/kg falls within the manufacturer's recommended intravenous dosage range of 1–4.5 mg/kg. The significant increases in blood pressure and heart rate

Figure 2. Cumulative ketamine dose (log scale) vs response curves for abolition of reaction to verbal commands, eyelash stimulation, and painful stimulation (trapezius squeeze).

observed with ketamine induction are also comparable to those previously reported in ASA class III and IV patients (25).

The hypertension and tachycardia accompanying ketamine induction may be dangerous in patients with essential hypertension, coronary artery disease, or intracranial mass lesions. Midazolam, by allowing hemodynamic stability without undue sympathetic stimulation, may be a useful alternative for induction of anesthesia in unstable ASA class III and IV patients. However, care must be taken to ensure that the dose of midazolam is sufficient. Previously reported induction doses (0.15–0.35 mg/kg) may be inadequate for many patients. Therefore, additional incremental doses of midazolam should be administered, if necessary, before proceeding with laryngoscopy, tracheal intubation, or surgery.

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## Potential of Systemic Morphine Analgesia in Humans by Proglumide, a Cholecystokinin Antagonist

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PRICE DD, VON DER GRUEN A, MILLER J, RAFII A, PRICE C. Potentiation of systemic morphine analgesia in humans by proglumide, a cholecystokinin antagonist. *Anesth Analg* 1985;64:801-6.

*Proglumide, a cholecystokinin antagonist, potentiates analgesia produced in rats by morphine and endogenous opiates, and appears to reverse tolerance in rats to opiate analgesia. Therefore, proglumide and other cholecystokinin antagonists may be clinically valuable. We have tested proglumide's possible opiate analgesic potentiating effects by examining, in volunteers, the effects of morphine and pro-*

*glumide on human pain visual analogue scale responses to 45-51°C skin temperature stimuli. Proglumide (50-100 µg intravenously) potentiated both the magnitude and duration of analgesia produced by small doses of morphine. This study provides indirect evidence for a cholecystokinin-opiate interaction in humans. Therefore, cholecystokinin antagonists such as proglumide may serve to potentiate exogenous or endogenous opiate action.*

**Key Words:** ANTAGONISTS, MISCELLANEOUS—proglumide.

Cholecystokinin octapeptide (CCK), a putative central nervous system neurotransmitter (1), has been shown to selectively antagonize opiate analgesia when administered systemically or intrathecally (2). These observations indicate that CCK may act physiologically as an endogenous opiate antagonist. If so, then administration of antagonists to CCK might result in potentiation of analgesia induced by endogenous or exogenous opiates, or both, and possibly might reverse tolerance to opiate analgesia. Watkins et al. (3) have recently tested these possible effects by systemic and intrathecal administration of proglumide, a selective CCK receptor antagonist, to opiate-naïve and opiate-tolerant rats. They found that administration of proglumide potentiated both systemic morphine analgesia and a form of footshock analgesia that is probably mediated by endogenous opiates. They also discovered that proglumide reversed morphine tolerance induced by either repetitive systemic or intrathecal administration of opiates.

The results of Watkins et al. indicated that CCK antagonists may be clinically valuable for potentiating opiate analgesia and for preventing or reversing the development of tolerance to opiates. However, appropriate human studies are critically important in

testing these effects. Therefore, we have tested the first of these possible effects: that proglumide facilitates the analgesic effects of morphine in humans. Although proglumide has been tested extensively in humans in the management of peptic ulcer disease (4), the doses used were much higher than those tested in the present study. No results have indicated that proglumide has any analgesic activity when administered alone. We now provide the first evidence that extremely low doses of proglumide powerfully facilitate the analgesic effects of morphine on experimental pain in humans.

### Methods

#### *Subjects*

Experimental subjects were 80 paid volunteers comprised of medical students, dental students, graduate students, and hospital staff personnel who gave informed consent to participate. The study was given IRB approval by the Committee on Human Research. The general purpose of the experiment and the methods of producing and responding to heat-induced pain were explained to the subjects. Subjects were 20-40 yr old, were in good physical health, and did not have symptoms or medical problems contraindicating administration of morphine. Subjects were naïve to this experimental paradigm and had never participated in previous studies of this kind. Each subject participated in a 6-8 hr experimental session under constant medical supervision. Subjects reclined on

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hospital beds throughout most of the duration of experimental sessions.

### Experimental Design

The major purpose of this study was to find a minimum proglumide dose that would facilitate morphine analgesia. Volunteer subjects were given a standard intravenous dose of morphine, combined 5 min later with a second intravenous injection of either saline or a given dose of proglumide. The second saline injection was given on a double blind basis, and subjects were randomly assigned to control (50% of subjects) or proglumide groups (50% of subjects). After 16 subjects were tested, the double blind was broken, and analgesic responses of control subjects were statistically compared with those of subjects who received proglumide. The range of doses that were tested, 10–100  $\mu$ g, is based on the rationale that extremely low proglumide doses (2–20  $\mu$ g/kg) powerfully facilitated systemic morphine analgesia in rats.

Five groups were included in the double blind trials: those subjects who received 0.04 mg/kg morphine sulfate plus saline ( $n = 17$ ); those who received 0.04 mg/kg morphine sulfate plus 10  $\mu$ g proglumide ( $n = 8$ ); those who received 0.04 mg/kg morphine plus 100  $\mu$ g proglumide ( $n = 8$ ); those who received 0.06 mg/kg morphine sulfate plus saline ( $n = 16$ ); and those who received 0.06 mg/kg morphine sulfate plus 50  $\mu$ g proglumide ( $n = 8$ ). Subjects in these groups read a consent form that stated that they would receive either 0.0, 2.8, 4.2, or 5.6 mg morphine sulfate combined with proglumide (10–100  $\mu$ g) or saline. In addition, 8 subjects were given 0.08 mg/kg morphine sulfate under a single-blind condition, i.e., they also were told they would receive either 0.0, 2.8, 4.2, or 5.6 mg morphine/70 kg body weight. This group was tested to complete a dose–analgesic response curve for morphine (Fig. 3), and thereby provide a means of further assessing quantitatively the facilitatory effects of proglumide. Finally, 7 subjects each were given 100  $\mu$ g proglumide in saline and were told the dose was 5 mg morphine. This group was tested in order to determine whether proglumide had any direct analgesic action when administered alone.

### Procedure for Administering and Responding to Experimental Pain

Experimentally induced pain was measured by having human volunteers make visual analogue scale (VAS) pain sensation intensity responses to 45, 47, 49, and 51°C temperatures delivered for 5 sec to 1-cm<sup>2</sup> areas on the ventral forearm. The stimuli were delivered by

a research assistant by means of a contact thermode system. The design of this system has been described previously (5). The different intensity stimuli were applied in random order, and each temperature was given two times at each testing session. Subjects responded to each of these stimuli by making marks along 15-cm visual analogue scales anchored at their right end by "the most intense pain sensation imaginable." This method of producing visual analogue scale responses to suprathreshold experimental heat pain has been validated recently as a ratio scale measure of both chronic and experimental pain (6). Subjects were tested before and at various designated times after drug administration (Fig. 2). Each subject's baseline measures of responses to temperature stimuli were based on averages of four VAS responses to each temperature stimulus intensity. Each subject's post-drug measures were based on averages of two VAS responses to each of four temperatures at each testing session.

### Data Analysis

The degree of analgesia was measured in each subject as the decrease in area under the 45–51°C stimulus–VAS response curve. This measure was computed by subtracting the area under the post-drug stimulus–response curve from the area under the baseline stimulus–response curve. The resulting value obtained from each subject was used as a repeated measure in an analysis of variance wherein different treatment groups were compared. Paired *t*-tests comparing each subject's area under the temperature stimulus–VAS response curve before and at specific times after drug administration also were carried out for particular treatment groups. The *t*-tests served to determine whether analgesia was present within a given treatment group at specific times after drug administration.

Analgesia also was computed in terms of percent of maximum possible effect for the purpose of making quantitative comparisons among analgesic responses of different treatment groups (Fig. 3). This value was computed for each treatment group as follows:

$$\frac{\text{Mean area under baseline stimulus-VAS response curve} - \text{Mean area under post-treatment stimulus-VAS response curve}}{\text{Mean area under baseline stimulus-VAS response curve}} \times 100 = \% \text{ maximum possible effect.}$$



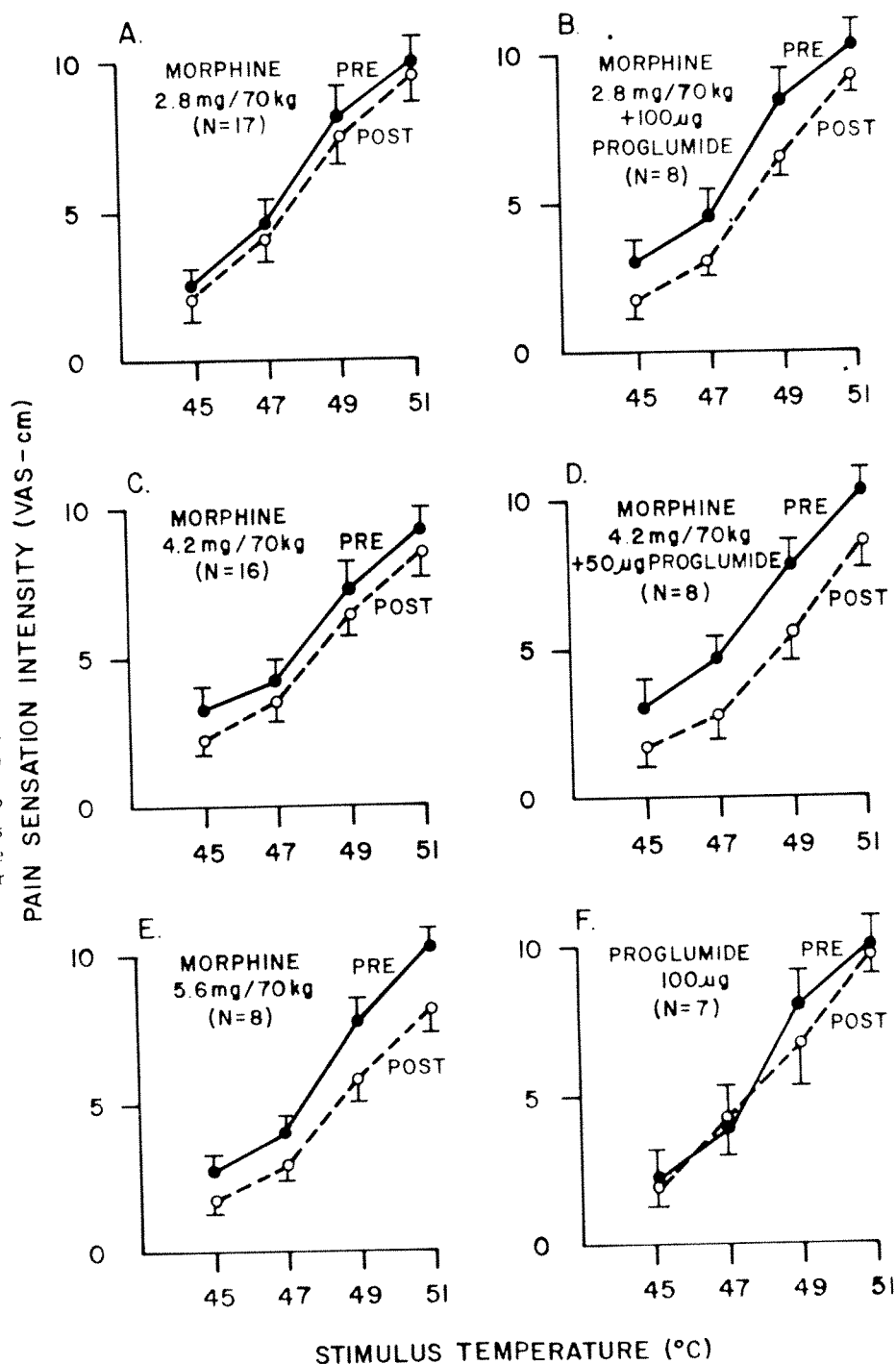


Figure 1. Nociceptive temperature stimulus-VAS functions before and after intravenous injection of morphine, proglumide, or both. Each point is the group mean ( $\pm$  SEM). Symbols: closed circles and solid lines refer to baseline stimulus-pain response functions, and open circles and dashed lines refer to stimulus-response functions averaged from testing sessions carried out 15 min, 45 min, and 1.5 hr after drug administration. The reductions in stimulus-response functions were statistically reliable for group data shown (B) ( $P < 0.05$ ), (D) ( $P < 0.01$ ), and (E) ( $P < 0.01$ ), but not in (A) ( $P > 0.02$ ) or (F) ( $P > 0.4$ ). Statistical tests were paired *t*-tests comparing each subject's areas under the stimulus response curve before and after drug administration.

## Results

### Proglumide Facilitation of Analgesia

No analgesic effects were found in the groups receiving 0.04 mg/kg morphine sulfate alone, 0.04 mg/kg morphine sulfate plus 10  $\mu$ g proglumide, or 100  $\mu$ g proglumide alone. Their responses to experimental pain were similar before and after drug administration (Fig. 1(A), (F), and Fig. 2, top). However, when ad-

ministered together, the combination of 100  $\mu$ g proglumide plus 0.04 mg/kg morphine sulfate produced definite analgesic effects (Fig. 1(B) and Fig. 2, top). The reduced pain VAS responses occurred throughout the 45–51°C stimulus range (Fig. 1(B)). The mean decrease in VAS responses of the group receiving 0.04 mg/kg morphine plus 100  $\mu$ g proglumide was statistically significant (analysis of variance,  $P < 0.001$ ) and was significantly greater than the mean change in

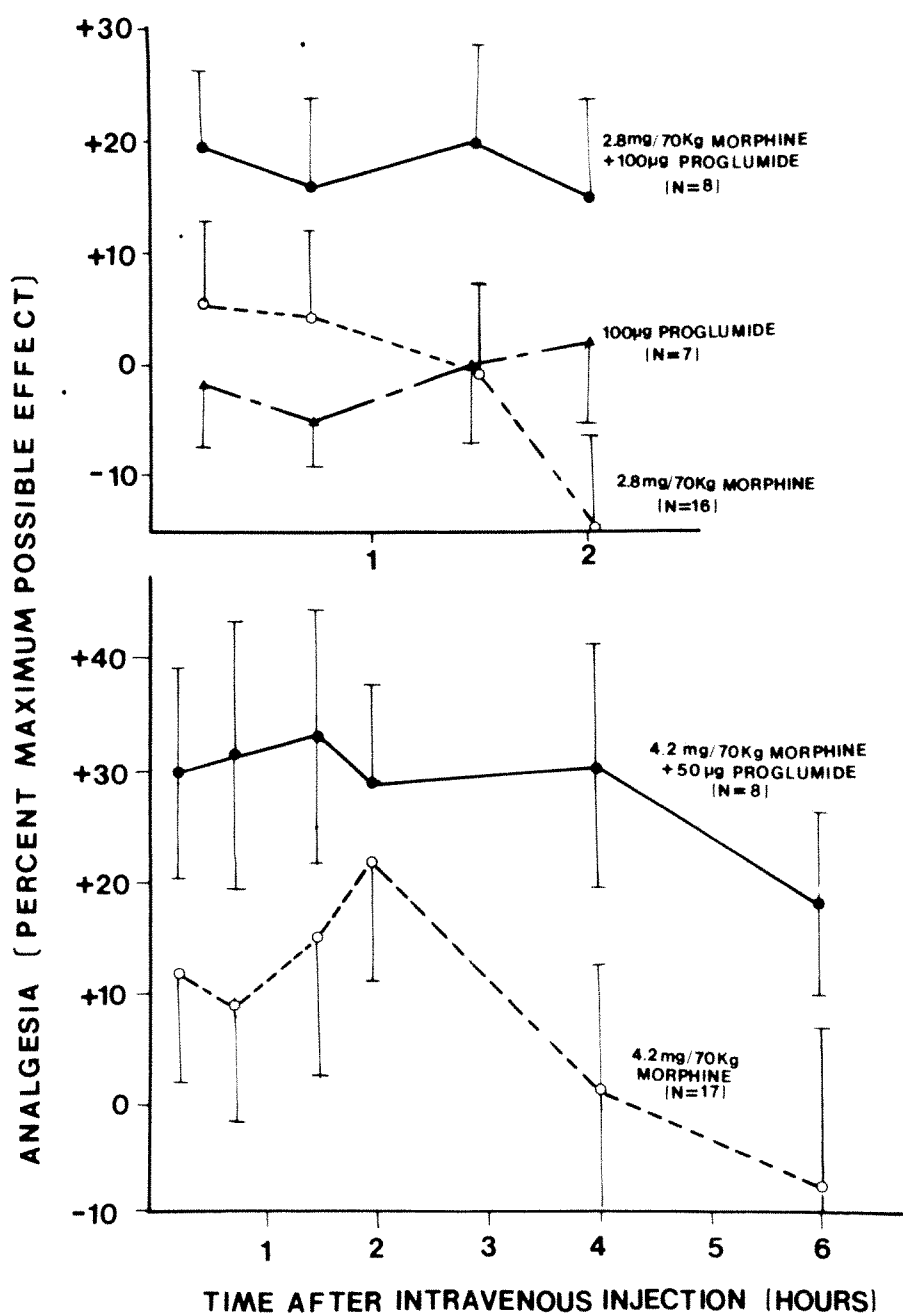


Figure 2. (Top) Enhancement of systemic morphine (0.04 mg/kg intravenous administration) analgesia by systemic proglumide (100 µg intravenous administration). Each point is the group mean level of analgesia expressed as % maximum possible effect. Symbols: filled circles, group receiving proglumide plus morphine; open circles, group receiving morphine only; closed triangles, group receiving proglumide only; vertical bars, one standard error of the mean (SEM). (Bottom) Enhancement of systemic morphine (0.06 mg/kg intravenous administration). As above, each point is the group mean level of analgesia expressed as % maximum possible effect (+1 SEM).

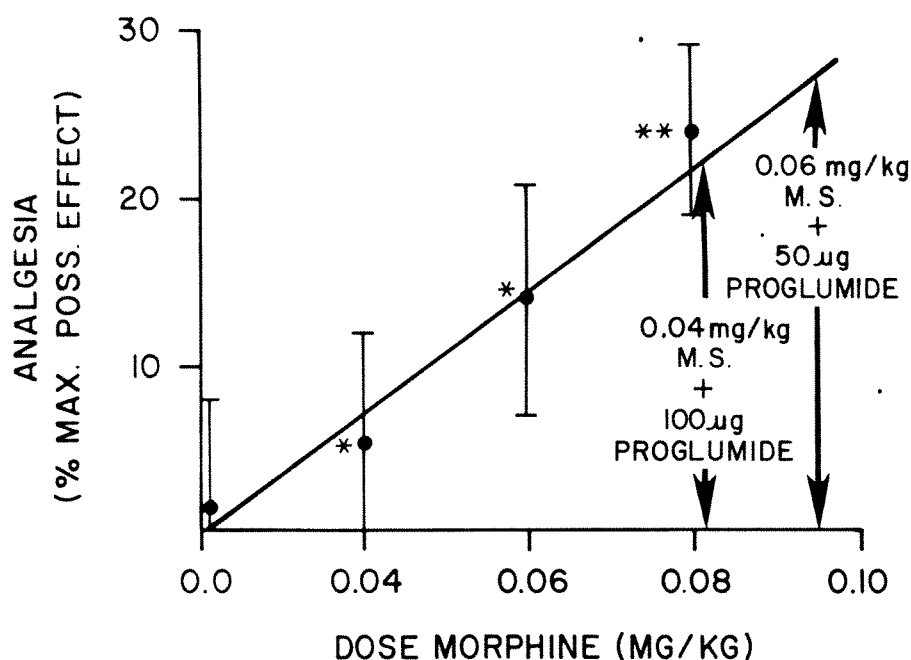
VAS responses of the group receiving only 0.04 mg/kg morphine sulfate ( $P < 0.001$ , analysis of variance). The analgesic effect lasted 2 hr in the group receiving 0.04 mg/kg morphine sulfate plus 100 µg proglumide.

Surprisingly, when this trial was repeated using a higher dose of morphine (0.06 mg/70 kg body weight), 100 µg proglumide neither facilitated nor suppressed the analgesic effects of morphine (analysis of variance,  $P > 0.2$ ). We then decided to test a lower dose of proglumide (50 µg).

The 50 µg dose of proglumide significantly poten-

tiated the analgesia produced by 0.06 mg/kg morphine throughout the 6 hr of testing (analysis of variance,  $P < 0.0001$ ). As can be seen in Figures 1(C) and (D) and Figure 2 (bottom), proglumide increased both the magnitude as well as the duration of analgesia produced by morphine. Subjects receiving both 50 µg proglumide and 0.06 mg/kg morphine had significantly lower VAS pain responses 6 hr after injection ( $P < 0.02$ , one tailed paired  $t$ -test), whereas subjects receiving only 0.06 mg/kg morphine were analgesic for less than 4 hr (Fig. 2, bottom).

Figure 3. Dose-response curves for effects of morphine on pain VAS responses to 45–51°C temperatures. As in Figure 2, the degree of analgesia is expressed as average % of decrease in area under the stimulus response curve. The analgesia responses are averaged from and collapsed across 15 min, 45 min, and 1.5 hr testing sessions because there are no differences in analgesic responses at these testing periods. The group receiving 0.04 mg/kg morphine plus 100  $\mu$ g proglumide and the group receiving 0.06 mg/kg morphine plus 50  $\mu$ g proglumide are indicated by vertical arrows.



A quantitative assessment can be made of the degree to which low doses of proglumide facilitate morphine analgesia. As can be seen in Figure 3, morphine reliably reduces VAS responses to experimental pain in a dose-dependent manner. This dose-response relationship can be used to determine the relative extent that analgesia was facilitated by proglumide. One hundred micrograms of proglumide facilitated a 0.04 mg/kg dose of morphine to an extent that was equivalent to 0.08 mg/kg morphine. Although the exact degree of facilitation cannot be ascertained, it is clear that adding 50  $\mu$ g proglumide to a 0.06 mg/kg dose of morphine results in an analgesia level approximately the same as that produced by 0.09 mg/kg of morphine.

## Discussion

Systemic administration of proglumide significantly potentiated the analgesic effects of systemic morphine. This potentiation cannot be accounted for by direct analgesic effects of proglumide alone, because proglumide in the absence of opiate administration produces no effect on experimental pain. One hundred micrograms of proglumide potentiated analgesia produced by 0.04 mg/kg morphine, but a lower proglumide dose (50  $\mu$ g) was required to potentiate analgesia produced by 0.06 mg/kg morphine. Although these different dose requirements appear somewhat perplexing, they are consistent with the work of Watkins et al. (3), who found a biphasic dose-response function in facilitatory effects of proglumide. They

found that lower doses of proglumide (0.002–0.02 mg/kg) produced a dose-related facilitation, and higher proglumide doses ( $> 0.2$  mg/kg) produced a dose-related attenuation of morphine-analgesia. In addition to this biphasic dose-response relationship, there may be an inverse relationship between the dose of morphine administered and the dose of proglumide that optimally facilitates morphine analgesia. The combination of such factors could account for the results of our study; this possibility should be tested in future experiments.

A likely mechanism of proglumide's potentiating effect on opiate analgesia is that of antagonizing endogenous CCK systems. The possibility that proglumide enhances morphine analgesia in humans because of a general systemic effect on bioavailability and pharmacokinetics cannot as yet be ruled out. However, this possibility is at variance with the observation of Watkins et al. (3) that intrathecal administration of very small amounts of proglumide (0.001–0.01  $\mu$ g) enhances the analgesia produced in rats by intrathecal administration of morphine (1  $\mu$ g in 0.5  $\mu$ g saline). The fact that extremely low doses of proglumide are effective in both species (20–40  $\mu$ g/kg in rats and, as in this study, 50–100  $\mu$ g in humans) indirectly supports the hypothesis that a similar mechanism of facilitatory effects of proglumide exists for both rat and human species.

The indirect evidence for a CCK-opiate interaction in humans is of great theoretical and potential practical interest. Cholecystokinin may function physiologically to oppose the analgesic effects of opiates.

Indeed, experiments that demonstrate CCK antagonism of opiate analgesia at spinal and supraspinal sites indicate that an opiate-CCK interaction may be a pervasive phenomenon in the CNS (1-3). A natural extension of this idea is that tolerance resulting from repetitive exposure to exogenous opiates may result from a compensatory increase in CCK system activity. This idea is supported by evidence that proglumide reverses tolerance to morphine analgesia (3).

There appear to be three potential clinical benefits from administration of CCK antagonists such as proglumide: facilitation of analgesia produced by exogenous opiates, facilitation of endogenous opiate analgesia, and reversal of opiate tolerance. The first of these possible benefits may be limited by the possibility that proglumide also facilitates side effects of morphine (7). The morphine doses used in the present study were too low to assess this possibility. Clinical and experimental studies must be done to clarify this issue. However, this possible limitation may or may not pose much of a problem in proglumide's possible facilitation of endogenous opiate mechanisms. For example, proglumide or other CCK antagonists might be given in conjunction with electroacupuncture treatments, because analgesia resulting from such treatments is likely to be at least partly mediated by endogenous opiates (8). It is of interest in this regard that Han et al. have found that CCK-antisera potentiate electroacupuncture analgesia in

rabbits (9). Finally, the potential use of CCK antagonists in reversal and potential prevention of narcotic tolerance has far reaching biomedical implications for the long-term management of pain in humans.

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## Reduction in Halothane MAC: Comparison of Morphine and Alfentanil

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Reduction in halothane MAC: comparison of morphine  
and alfentanil. *Anesth Analg* 1985;64:807-10.

*The anesthetic potency and effectiveness of alfentanil and morphine were established by determining the effects of increasing drug doses on the alveolar anesthetic requirement of halothane to maintain a constant anesthetic (MAC) level. Six selected doses of alfentanil and four of morphine were administered to groups of mechanically ventilated rats anesthetized with halothane. Alfentanil was given as a loading dose followed by an intravenous infusion of  $0.01\text{--}100\ \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , and morphine was administered as a subcutaneous dose of  $4\text{--}20\ \text{mg/kg}$ . The reduction in halothane*

*requirement after morphine was biphasic, with a rapid linear increase occurring up to an  $8\ \text{mg/kg}$  subcutaneous dose, followed by a further, slower reduction in halothane requirement after doses of  $8\text{--}20\ \text{mg/kg}$ . At a  $20\ \text{mg/kg}$  dose, the halothane MAC was reduced approximately 84%. With alfentanil, a curvilinear reduction in halothane MAC occurred up to an alfentanil dose of  $15\ \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , where a 48% reduction was found. Larger doses produced severe truncal, chest wall, and abdominal rigidity, precluding adequate ventilation and the determination of MAC.*

**Key Words:** ANALGESICS—alfentanil. ANESTHETICS, VOLATILE—halothane. POTENCY, ANESTHETIC—MAC.

Although morphine has been clinically observed to produce essentially complete anesthesia, animal studies have documented a maximal 65% reduction in enflurane concentration by morphine of motor response to tail clamp (1). Sufentanil, a more potent narcotic, produces nearly complete anesthesia, reducing halothane MAC by 90% (2). The contribution of alfentanil, a derivative of fentanyl more potent than morphine, to the MAC of halothane has not been determined. This study compared the reduction in the MAC of halothane produced by morphine and alfentanil in rats.

### Methods

The reduction of halothane MAC was determined as a measure of the potency of alfentanil and morphine. Fifty-nine male Sprague-Dawley rats weighing  $303 \pm 32\ \text{g}$  (mean  $\pm$  SEM) were anesthetized with 3.5% hal-

othane in oxygen for 3–5 min. Tracheal intubation was accomplished with an 18-gauge polyethylene catheter. During cannulation of the femoral artery and vein with PE50 tubing, the animal breathed halothane (1.5%) spontaneously. The concentration of halothane in the inspired gas was then reduced to 1%, and ventilation was controlled with a Harvard animal respirator. Rectal temperature was measured with a Yellow Springs thermistor and maintained at  $37 \pm 1^\circ\text{C}$  with a thermal mattress and heating lights. Arterial blood gases were measured to ensure normal  $\text{PO}_2$ ,  $\text{PCO}_2$ , and pH. Mean arterial pressure and ECG were monitored to ensure hemodynamic stability.

MAC was measured by the method of Eger et al. (3) using a tail clamp technique; a response was considered positive only when gross movement of the head, extremities, or body took place. Halothane concentrations were adjusted in decrements of 0.1%, until a positive response was obtained, allowing 15-min intervals for equilibration (4). MAC was considered to be the concentration midway between the highest concentration allowing movement and the lowest concentration producing no movement. The MAC of halothane alone initially was measured and then determined in the same manner either during infusions of alfentanil or after subcutaneous doses of morphine.

Alveolar gas samples were obtained from a PE10

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Table 1. Effect of Alfentanil Dose on Halothane MAC

MAC	Dose ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	Decrease (%)	Group % $\downarrow \pm \text{SEM}$
0.69	0.001	0	$0 \pm 0$
0.69	0.01	0	
0.59	0.01	0	
0.88	0.1	19	$4.6 \pm 2.6$
0.59	0.1	1	
0.71	0.1	3	
0.82	0.1	1	
0.81	0.1	0	
0.80	0.1	8	
0.69	0.1	0	
1.03	1	20	$15.8 \pm 3.5$
0.88	1	33	
0.59	1	5	
0.71	1	17	
0.82	1	24	
0.81	1	9	
0.80	1	14	
0.69	1	4	
0.76	5	28	$19.4 \pm 3.0$
0.66	5	9	
0.66	5	14	
0.66	5	15	
0.74	5	15	
0.82	5	27	
0.80	5	28	
0.69	10	24	$27.2 \pm 3.7$
1.03	10	31	
0.74	10	39	
0.66	10	12	
0.66	10	26	
0.74	10	31	
0.73	15	77	$47.7 \pm 6.4$
0.66	15	33	
0.71	15	37	
0.82	15	44	
0.81	15	44	
0.69	15	51	

polyethylene catheter introduced through and beyond the endotracheal tube until obstruction was met and then withdrawn 1–2 mm. The gas samples were drawn into glass syringes over a 3–5 min interval after the time of tail clamping and were assayed for halothane concentration on a Hewlett-Packard Model 5750 chromatograph with a flame ionization detector.

A constant intravenous infusion of alfentanil from 0.01–100  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  was administered after an intravenous bolus equivalent to 10 min of infusion (i.e., a 300-g rat would receive an initial bolus of 0.3  $\mu\text{g}$  followed by an infusion of 0.1  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ). Groups of three to eight animals were studied at each

Table 2. Plasma Levels of Morphine and Alfentanil

Morphine		Alfentanil	
Dose ( $\text{mg}\cdot\text{kg}^{-1}$ )	Plasma concentrations ( $\text{ng}\cdot\text{ml}^{-1}$ )	Dose ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	Plasma concentration ( $\text{ng}\cdot\text{ml}^{-1}$ )
2	65	15	104
8	243	20	179
12	385	30	289
20	649	50	379
		100	771

of the six selected doses of alfentanil. Each animal received at least one infusion rate. Each new infusion rate was preceded by a bolus dose of alfentanil. Doses of morphine of 4, 8, 12, or 20 mg were administered subcutaneously. The subcutaneous route was chosen because of extensive experience with this mode of administration. Plasma levels of alfentanil were measured using gas liquid chromatography (performed by Bioanalytical Laboratories of Janssen Pharmaceutica; assay has an error rate of  $< 4\%$ ). Morphine levels were measured by high performance liquid chromatography (5) at the determination of MAC. Inspired halothane concentrations were reduced in increments of 0.1% every 20–30 min, and the response to tail clamp assessed until a positive response was obtained. The mean and SEM of the decreased MAC attained in each treatment group were determined and compared by one-way analysis of variance.

## Results

The MAC for halothane was  $0.76 \pm 0.02\%$  in rats receiving alfentanil and  $0.80 \pm 0.03\%$  in those receiving morphine, both of which are similar to previous observations in rats (6). In preliminary studies, an attempt was made to determine the reduction in cyclopropane MAC with morphine (7) or sufentanil (2). Subcutaneous doses of 2, 4, and 8 mg/kg morphine reduced MAC by 22, 33, and 55%, respectively (7). With sufentanil and cyclopropane, cardiovascular collapse occurred, precluding MAC determinations. This possibly was the result of a diminished catecholamine response during sufentanil administration. A similar response was anticipated with alfentanil, so the reduction in halothane MAC was investigated.

In the animals receiving alfentanil, there was no effect on MAC until more than 0.1  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  had been given. Thereafter, with progressively increasing doses of alfentanil, a nonlinear reduction of MAC occurred. The reduction of MAC observed during alfentanil infusion was consistent among the rats in a given group, and dose-response data are presented

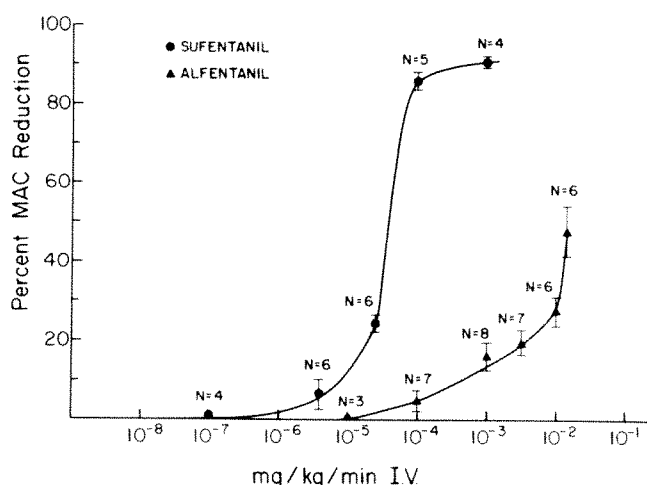


Figure 1. Reduction of halothane minimal alveolar concentration observed with progressively increasing alfentanil and sufentanil doses.

in Table 1. The maximal reduction in MAC that could be measured after alfentanil doses was 48% at a  $15 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  dose (Fig. 1). The plasma concentration of alfentanil at this point was  $104 \text{ ng}\cdot\text{ml}^{-1}$ . At doses of alfentanil between 15 and  $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , 7 of 15 rats developed chest wall and abdominal rigidity, precluding determination of MAC, but 8 of the 15 animals did not become rigid. In animals receiving infusions of  $25\text{--}100 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , all rats developed rigidity. Plasma concentrations of alfentanil increased linearly at higher doses (Table 2).

In contrast there was a rapid linear reduction in the MAC of halothane by morphine up to  $8 \text{ mg/kg}$  and a slower rate of reduction in the MAC from  $8\text{--}20 \text{ mg/kg}$  of morphine. At the highest dose, the reduction of MAC by morphine was 84% (Fig. 2), and the response may have been approaching a plateau. Neither seizures nor chest wall rigidity occurred during the experiments with morphine. Plasma concentrations of morphine at the time of MAC determination are in Table 2. Plasma concentrations increased linearly with dose. Heart rate, blood pressure, and peripheral perfusion were unchanged in both groups of animals, and arterial blood gases remained within the normal range.

## Discussion

The development and proliferation of new narcotic agents have been enhanced by the need for drugs producing complete anesthesia while maintaining hemodynamic stability. Unlike sufentanil, which produced greater than 90% reduction in halothane MAC in rats without serious side effects (2), alfentanil

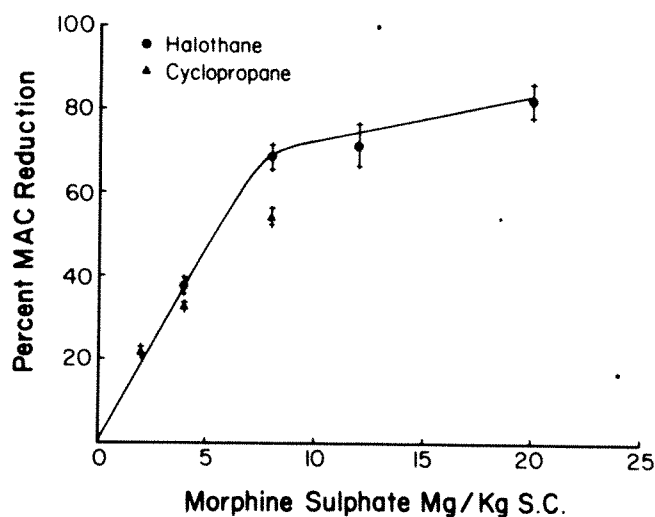


Figure 2. A linear reduction of halothane minimal alveolar concentration occurs with morphine dose up to  $8 \text{ mg/kg}$  subcutaneously with a slower reduction between 8 and  $20 \text{ mg/kg}$ . A similar reduction in the MAC of cyclopropane is also noted.

produces rigidity at doses giving only a 48% MAC reduction of halothane. Thus higher-dose alfentanil anesthesia, although possibly capable of greater reduction in MAC, requires the addition of a neuromuscular blocking drug (8) and therefore cannot be measured in the unparalyzed animal studied in this experiment. Thus whether or not the alfentanil dose-response curve would reach a plateau or result in complete anesthesia, like that of sufentanil, remains uncertain.

Fentanyl, when administered via a constant infusion to dogs, decreases the MAC of enflurane by only 65% (9), and therefore appears to be an incomplete anesthetic in dogs. However, this finding is in contradistinction to the satisfactory use of fentanyl as the sole anesthetic in human cardiac surgery (10) and may be the result of species variation or a specific interaction between fentanyl and enflurane.

In the present study, morphine, in contrast to alfentanil, produced a dose-dependent reduction in the halothane MAC, achieving a maximal effect of 84% depression of halothane MAC. Therefore morphine, like sufentanil, can produce almost complete anesthesia in rats. The difference between the magnitude of our results and those previously reported (1,2) is probably caused by differences in anesthetic agents used and on the mode of drug administration. The dose required for equivalent MAC reduction is 100 times greater with alfentanil than with sufentanil (Fig. 1). Almost complete anesthesia can be produced by morphine or sufentanil, but no more than a 47% reduction in halothane MAC could be achieved with alfentanil in the absence of neuromuscular blockade.

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## Respiratory Sinus Arrhythmia during Recovery from Isoflurane–Nitrous Oxide Anesthesia

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DONCHIN Y, FELD JM, PORGES SW. Respiratory sinus arrhythmia during recovery from isoflurane–nitrous oxide anesthesia. *Anesth Analg* 1985;64:811–15.

*Heart rate and respiratory patterns were monitored in ten ambulatory female patients undergoing elective laparoscopy. The patients were anesthetized with isoflurane–nitrous oxide. An index of cardiac vagal tone determined from the heart rate pattern by quantifying the amplitude of respiratory sinus arrhythmia was elevated over four 10-min periods: before induction of anesthesia; during maintenance*

*of anesthesia; upon arrival in the recovery room; and 20–30 min later when the patient was fully conscious. All ten patients' vagal tones were lowest during maintenance of anesthesia. During the recovery periods vagal tone increased and approached the conscious level. On-line analysis of respiratory sinus arrhythmia may provide a physiological index of the level of anesthesia and the rate of recovery.*

**Key Words:** HEART, ARRHYTHMIAS—sinus. ANESTHETICS, VOLATILE—isoﬂurane.

Monitoring ECG during anesthesia provides for the detection of arrhythmias, myocardial ischemia, possible electrolyte abnormalities, and some indication of myocardial O<sub>2</sub> demand (rate–pressure product). However, little attention has been focused on the information regarding central nervous system status that can be derived from the quantification of heart rate variability during anesthesia. Because centrally mediated neural mechanisms contribute to the beat-to-beat variability of heart rate, monitoring changes in heart rate during anesthesia and in the immediate postanesthetic period may provide important clinical information on the influence of anesthesia on the central nervous system. This information is available by data analysis of information from the noninvasive ECG electrodes.

This study approached the clinical question of the impact of anesthesia on respiratory sinus arrhythmia (RSA), a centrally mediated component of heart rate variability, which is characterized by heart rate acceleration during inspiration and deceleration during expiration. In their experiments with cooling of the

vagus, Katona and Jih (1) suggested that measurement of RSA amplitude could be used as an estimate of parasympathetic control of the heart. This hypothesis assumes that the amplitude of RSA can be easily quantified. Unfortunately, the heart rate pattern is influenced by many factors, and an accurate determination of RSA amplitude requires a sophisticated statistical approach. Porges et al. (2) have demonstrated an accurate method of quantifying the RSA amplitude by applying time series statistical techniques. This method quantifies the RSA amplitude after the complex heart rate trend, upon which RSA is superimposed, has been removed. To emphasize the relationship between RSA amplitude and vagal tone, the variance of the heart rate pattern in the frequency band of respiration (i.e., RSA) is being used and labeled  $\dot{V}$ .

### Materials and Methods

Ten female patients scheduled for elective ambulatory laparoscopy at Michael Reese Hospital were included in this study. Patients ranged in age from 21–63 yr. Except for one patient with mild hypertension treated with low doses of propranolol, all patients were ASA class I. No premedications were given.

The patients were treated with 3-mg doses of curare to avoid fasciculations, and anesthesia was induced with 4 mg/kg thiopental followed by 100 mg of succinylcholine to facilitate tracheal intubation. Nitrous oxide, 70%, in 30% oxygen and isoflurane were

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used for maintenance of anesthesia. The concentrations (vol%) of inhaled gases and the partial pressures of expired gases were monitored with a Perkin-Elmer mass spectrometer. Ventilation was controlled with a tidal volume of 10 ml/kg and a respiratory rate adjusted to maintain an end-tidal  $PCO_2$  of 40 torr. ECG and respiration tracings were displayed on a Hewlett-Packard monitor. The output of the ECG and respiratory monitor was stored on an FM tape recorder (Vetter C-4) and analyzed off-line. Details for the statistical procedures are in the appendix.

Data were recorded during four 10-min sessions, the first before anesthesia, the second when end-tidal isoflurane reached 18 torr (approximately 2 MAC), the third immediately after arrival in the recovery room, and the fourth 20–30 min later. The second period measurements were recorded prior to the surgical procedure. Behavior and alertness of the subjects were assessed and recorded by the first author. All patients were discharged from the hospital within 5 hr after arrival in the recovery room. The output from the FM tape recorder was played into a PDP 11/34 minicomputer to detect the peak of the R wave of the ECG, and to time sequential heart periods (i.e., R–R intervals) to the nearest msec. Respiratory amplitude (i.e., changes in chest circumference) was sampled at 2 Hz. Data were analyzed within each sequential 30-sec epoch during the four 10-min periods of measurement. The mean  $\dot{V}$  (i.e., RSA amplitude) and heart period for each patient within each period of measurement were calculated. Analysis of variance tested the differences in heart period and  $\dot{V}$  among the four periods of measurement. A value of  $P < 0.05$  was used for statistical significance.

## Results

All 10 subjects had their lowest  $\dot{V}$  during maintenance of anesthesia. One patient, not included in the above analysis, had glycopyrrolate 0.2 mg intramuscularly as premedication. This patient had a very low  $\dot{V}$  before anesthesia was induced, and the  $\dot{V}$  decreased further during 2 MAC isoflurane.

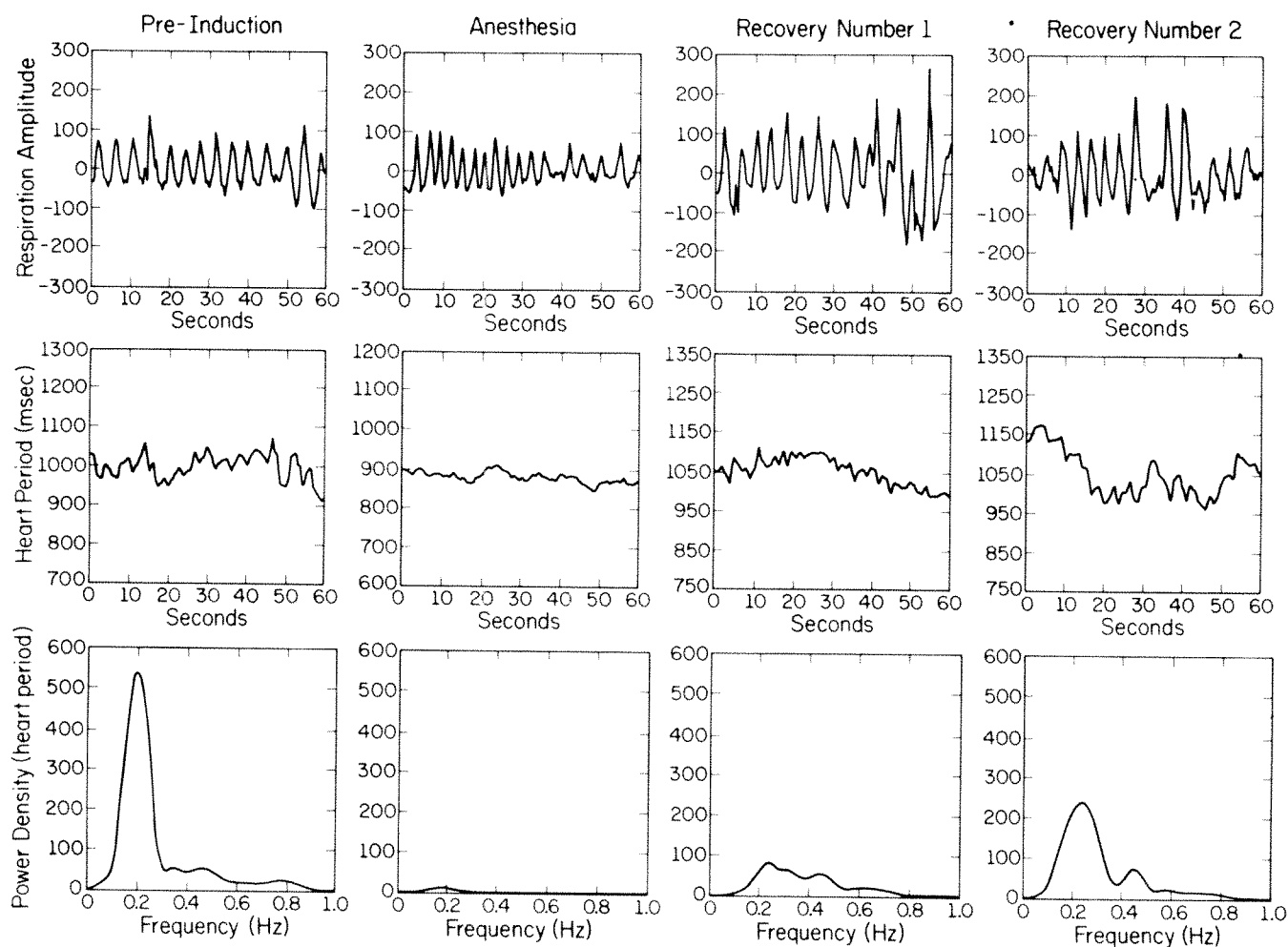
Blood pressure did not change by more than 20 torr during the procedure and was stable in the postoperative period. Figure 1 illustrates data from one patient during the periods of measurement. The top two rows illustrate one min of simultaneously recorded respiratory amplitude and heart rate. The bottom row illustrates the power density estimates for the heart period pattern derived from spectral analysis. Within the frequency band of respiration (0.12–0.40 Hz), the spectrum of power density estimates has a pronounced peak before induction of

anesthesia and is virtually unidentifiable during anesthesia maintenance. The peak reappears during the first recovery period and becomes pronounced during the second recovery period. Note the similarity of the respiratory pattern during the four periods of measurements and the dissociation between the heart period and respiratory patterns during anesthesia.

The mean  $\dot{V}$  before surgery was 5.7, and during 2 MAC isoflurane, mean  $\dot{V}$  decreased to 1.6, a depression from the control value of approximately 71% (see Fig. 2). In the immediate postoperative period,  $\dot{V}$  increased to 4.0, and later during recovery, when patients were more alert,  $\dot{V}$  increased to 5.0, approaching the preoperative control level of 5.7. Analysis of variance confirmed that  $\dot{V}$  was significantly different among the four periods of measurement ( $f(3,36) = 17.5$ ,  $P < 0.0001$ ). Duncan multiple range tests were used to identify the specific paired differences. The preinduction base level was significantly different than the levels during maintenance of anesthesia and during first recovery period measurements.

Heart period was not sensitive as an indicator for the CNS status. Analysis of variance of the heart period data failed to identify a significant difference among the periods of measurement ( $f(3,36) = 1.97$ ,  $P > 0.1$ ). There was a tendency for heart period to be shorter during maintenance of anesthesia (707 msec) than before induction (895 msec). As illustrated in Figure 2, anesthesia produced a change from the preinduction control level of 17% in the heart period, in contrast to a 71% reduction in the  $\dot{V}$  estimate.

An alternative way of assessing the sensitivity of the vagal tone index to anesthesia is to use methods employed in screening tests. The vagal tone index could be viewed as a test employed to detect the state of anesthesia. The sensitivity of  $\dot{V}$  could be evaluated by identifying the percentage of subjects detected by  $\dot{V}$  who are anesthetized. The specificity could be evaluated by identifying the percentage of subjects correctly labelled by  $\dot{V}$  who are not equilibrated with 2 MAC isoflurane. For example, because the control level vagal tone was 5.7 (SD 0.7), a criterion level could be established statistically at three standard deviations below the mean or a  $\dot{V}$  approximately 3.6. The selection of three standard deviations is based upon the assumption that the vagal tone is normally distributed in the population, and that a value less than three standard deviations from the mean would occur in the normal population with a frequency of approximately 1 in 1000. Using this criterion, all ten subjects had a vagal tone during 2 MAC isoflurane anesthesia of less than 3.6, and all ten subjects had a vagal tone during the baseline control condition of greater than 3.6. Thus with the use of this arbitrary



criterion, the sensitivity of the vagal tone index is 100%, and the specificity is 100%. When the two recovery periods are compared with baseline control, the number of patients with a  $\dot{V}$  of less than 3.6 decreases, as would be expected by the observed individual differences. Table 1 lists the frequencies of high and low vagal tone within each of the four evaluation conditions.

## Discussion

Our data demonstrate that the amplitude of RSA ( $\dot{V}$ ) decreases in the course of isoflurane-nitrous oxide anesthesia and increases in the recovery period. As early as 1935, during experiments on dogs, Samann (3) noticed that RSA disappeared during the induction of ether anesthesia. McCrady et al. (4) reported that the usual pattern of RSA diminished in the course of halothane anesthesia in dogs, and even disappeared in stage 3. The authors suggested that RSA may provide a quantitative means for monitoring the level of anesthesia.

Figure 1. An example in one subject of the influence of isoflurane-nitrous oxide anesthesia on respiratory amplitude (i.e., changes in chest circumference associated with breathing), heart period, and the heart period spectrum. The heart period and respiratory amplitude data are examples of data simultaneously collected for 60 sec in each of the four periods of measurement.

More recently, Yamamura et al. (5) demonstrated that halothane depressed vagal tone to 30% of the control level in cats, and that this depression of vagal tone was dose-dependent. Vagal tone was evaluated by direct recordings of the action potentials from the vagus.

Since RSA was first described by Ludwig in 1847 (6), there have been many investigations evaluating potential mediating mechanisms. A number of hypotheses have been presented that relate RSA to vagal mechanisms. There is the possibility of a central "indicator" from the respiratory center to a cardiovascular center (7) that rhythmically modulates vagal efferent output at the breathing frequency. Stretch reflexes from the lung may cause reflex vagal depres-

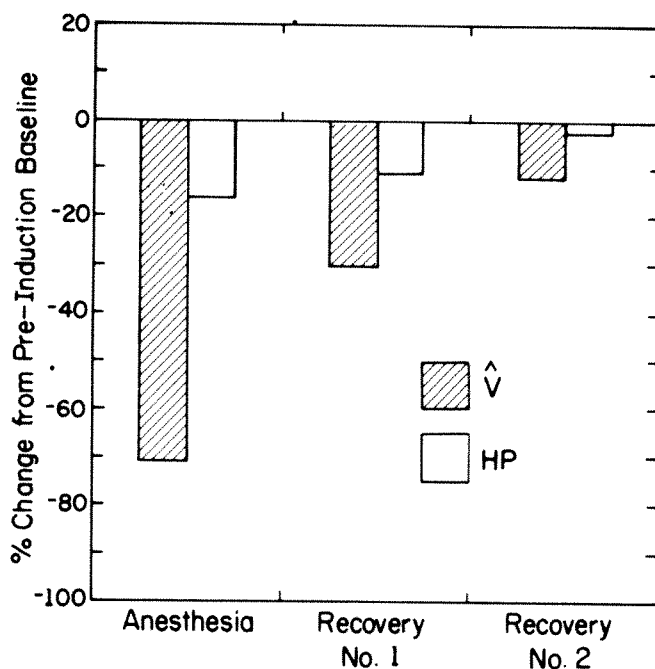


Figure 2. The mean % change from preinduction baseline of the amplitude of respiratory sinus arrhythmia (V) and heart period (HP) for ten subjects.

sion (8). Baroreceptor reflexes may be induced by changes in thoracic pressure due to respiration (9). Finally, the answer may lie in some combination of the preceding hypotheses (10).

Recording from cardiac vagal efferents indicates that the neural output of the vagal fibers is inhibited during inspiration and is released from inhibition during expiration (11). Moreover, during expiration, baroreceptor and chemoreceptor stimuli elicit a prompt bradycardia, whereas during inspiration these responses are blocked or attenuated (12). Recent research on the neural pathways of vagal cardio-inhibitory neurons show a respiratory-related pattern of discharge with the primary efferent action on the heart occurring during expiration. This has been demonstrated in cats and rabbits (13).

If there is no vagal influence on the heart there can be no RSA (14). The greater the cardiac vagal tone, the more pronounced the difference in heart rate between inspiration and expiration; the greater the cardiac vagal tone, the greater the amplitude of RSA. Thus the accurate measurement of RSA amplitude provides a peripheral manifestation of the influence of vagal cardio-inhibitory neurons on the heart.

Several studies have linked the amplitude of RSA with central nervous system status. Lowensohn et al. (15) found that normal cyclic changes in heart rate were reduced in the presence of severe brain damage and that variability decreased rapidly as intracranial

Table 1. Frequency of High and Low Vagal Tone within each of the Four Evaluation Conditions

Vagal Tone	Baseline	Anesthesia	Recovery (1)	Recovery (2)
High (> 3.6)	10	0	3	8
Low (< 3.6)	0	10	7	2

Low vagal tone is defined as values lower than three standard deviations from the mean of the control baseline condition.

pressure increased. Kero et al. (14) described the decreased heart rate variation in decerebration syndrome. In animal studies, transection of the brainstem anterior to the pons did not abolish RSA, but if the transection was in the pons anterior to the medulla, no RSA could be detected (16).

Joel and Samueloff (17) studied heart rate activity under conditions of diffusion respiration in dogs when peripheral respiratory movements and efferent feedback were eliminated by succinylcholine. Heart rate fluctuated rhythmically in a pattern similar to the prior respiratory rate. However, when centrally generated respiration impulses were eliminated by our deepening the level of anesthesia, RSA disappeared.

Until recently most methods employed to assess RSA were manual (i.e., peak to trough measure from a tachograph). However, an accurate method to quantify RSA may be implemented with the aid of a mini-computer that measures the time between sequential R-waves of the ECG with msec accuracy and extracts the amplitude of RSA. Although the analysis procedure described in this paper was conducted off-line, a real time analysis of V may be obtained by an on-line monitor. A vagal tone monitor has been developed to quantify the amplitude of RSA (i.e., V) on-line. Details regarding this monitor can be obtained from Delta-Biometrics, Inc., 4805 Enfield Drive, Bethesda, MD 20814.

Determining the depth of anesthesia clinically has never been an exact science. Such commonly used signs as movement, increased blood pressure, pulse, frequency of respiration, pupil size, and diaphoresis may all be blocked or attenuated by nonanesthetic drugs, i.e., propranolol, anticholinergics, muscle relaxants. Although multilead EEGs may help with the problem, they are expensive and difficult to interpret. Utilizing information derived from the heart rate pattern may be of benefit in this regard. The obstetrician in the delivery room evaluates fetal well-being by the variation in the fetal heart rate, rather than by the heart rate itself. Parer (18) suggests that the changes in fetal heart rate were a "result of numerous, sporadic inputs that travel from various areas of the cen-



tral cortex to the cardiac integratory centers in the medulla and then transmitted down the vagus."

At first we chose to study only one drug, isoflurane-nitrous oxide, which indeed had a measurable effect on RSA. Our use of pentothal should be noted, although we feel that after 15 min, when we took our measurements, its hypnotic effect was minimal. However, we cannot rule out the use of positive pressure breathing and its influence on RSA, although Joel and Samueloff (17) suggested that peripheral respiratory movements had no effect on RSA. Finally, it remains to be determined whether our results apply to other anesthetic agents.

*Appendix.* The time series statistic employed in this experiment required that the data were sequences of events occurring at equally spaced intervals in time. Therefore, the interbeat intervals were converted into a time-based sequence of successive 500-msec windows. For each successive 500-msec window, the succeeding heart period associated with the first R-wave in the window was used as the estimate of heart period. To remove the complex trend, a 21-point cubic polynomial was moved stepwise through the heart period data. The moving polynomial produced a smooth pattern characterizing the trend, which was subtracted from the original time series to generate a residual series free from trend. The moving polynomial procedure functioned as a high-pass filter with a low frequency cutoff of approximately 0.095 Hz (see Bohrer and Porges [19]). Because RSA is dependent upon breathing frequencies, the natural logarithm of the variance of the heart rate pattern within the frequency band of 0.12–0.40 Hz (i.e., approximately 7–24 cycles per min) was calculated for the  $\hat{V}$  estimate of vagal tone. The mean of sequential heart periods also was calculated.

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## Temperature and Ventilation after Hypothermic Cardiopulmonary Bypass

Robert N. Sladen, MB, MRCP(UK), FRCP(C)

SLADEN RN. Temperature and ventilation after hypothermic cardiopulmonary bypass. *Anesth Analg* 1985;64:816-20.

*Rewarming in the postoperative period after hypothermic cardiopulmonary bypass is often associated with hemodynamic and ventilatory instability. Temperature changes,  $P_{aCO_2}$  values, and delivered mechanical ventilation were observed for the first 12 hr in the intensive care unit in 73 patients who had undergone cardiac surgery with hypothermic cardiopulmonary bypass. Mean rectal temperature increased from 34.7 to 38.3°C over the first 8 hr after admission to the intensive care unit ( $P < 0.001$ ). The tem-*

*perature curve was sigmoid rather than linear, and the most rapid rate of temperature increase occurred 2-4 hr after admission. During rewarming, the most common abnormality of  $P_{aCO_2}$  on mechanical ventilation was acute respiratory acidosis ( $P_{aCO_2} > 45$  mm Hg,  $pH < 7.35$ ), which occurred in 42% of patients. This suggests that ventilatory management in the early postoperative period after hypothermic cardiopulmonary bypass should be carefully adjusted to the increased metabolic rate during rapid rewarming.*

Key Words: ANESTHESIA—cardiovascular. HYPOTHERMIA—anesthetic.

In 1963, J. Francis Damman, JR, MD, wrote, "Pulmonary insufficiency occurs to some degree in almost every patient undergoing cardiac surgery . . . respiratory acidosis constitutes a well-recognized hazard postoperatively." Dr. Damman used this observation to advocate routine mechanical ventilation after cardiac surgery (1). However, clinical experience suggests that postoperative mechanical ventilation has not eliminated the problem of respiratory acidosis, because ventilatory requirement is markedly affected by the temperature changes that occur after hypothermic cardiopulmonary bypass (CPB). Despite rewarming on CPB, we have observed central temperatures (nasopharyngeal and rectal) to be in the range of 34-35°C on admission to the intensive care unit (ICU). Decrease in nasopharyngeal temperature after separation from CPB has been documented by others (2,3). Over the next 12 hr temperature increases above normal, to the range of 38-40°C. Hypercapnia results unless minute ventilation is increased, presumably on the basis of an increase in carbon dioxide ( $CO_2$ ) production.

A prospective study was therefore devised to quan-

titate the temperature increase in the postoperative period after hypothermic CPB; define factors that might predict the pattern of rewarming; and determine the incidence of respiratory acidosis when patients are being mechanically ventilated during rewarming.

### Methods

Seventy-three patients undergoing cardiac surgery over a six-week period were studied. Patients undergoing nonhypothermic cardiopulmonary bypass (e.g., ventricular mapping); short, uncommon procedures (e.g., septal myomectomy); and patients who had severe systemic disease or who had major complications in the early postoperative period were excluded. Because no alterations were made to their anesthetic, surgical, or postoperative management, informed consent was not considered necessary by the institutional human subjects committee.

Patients were anesthetized with high-dose narcotics (fentanyl, morphine, or hydromorphone), pancuronium, and 100% oxygen. Temperature was monitored with nasopharyngeal and rectal probes (Yellow Springs); the telethermometers were previously calibrated against a mercury thermometer. Cardiopulmonary bypass was instituted via a bubble oxygenator (Harvey) primed with lactated Ringer's solution, with flows between 40-50  $ml \cdot kg^{-1} \cdot min^{-1}$ . Local myocardial hypothermia was provided by continuous pericardial

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irrigation, in addition to the use of cold cardioplegia. Moderate whole-body hypothermia was obtained by cooling on CPB, guided by nasopharyngeal temperature to a nadir of approximately 30°C. About 10 min prior to aortic cross-clamp release, warming was begun in order to attain a zenith of approximately 37°C just prior to weaning off CPB. Sodium nitroprusside was used to facilitate active fluid replacement and control hypertension after separation from CPB.

In the ICU, patients were sedated and placed on controlled mechanical ventilation for 12–18 hr after cardiac surgery. Mechanical minute ventilation was provided by a tidal volume ( $V_T$ ) of 12–15 ml/kg at a ventilator rate ( $f$ ) of 6–10 breaths/min, to achieve an arterial pH in the normal range (7.35–7.45). Subsequent ventilator changes were made on the basis of sequential arterial blood gas values drawn every 1–2 hr. Blood gases were measured at 37°C and then corrected to actual patient temperature. Only rectal temperature was monitored in the ICU.

The following data were collected for each patient: sex, age, body surface area (BSA), and nature of surgery. Variables of CPB technique that could possibly affect postoperative temperature changes were documented. These included total duration of CPB, times of cooling and warming on CPB, and nadir and zenith nasopharyngeal temperature on CPB.

Observations were made for the first 12 hr after surgery. In each case, rectal temperature was noted every 20 min, the values of all corrected arterial blood gas tensions (ABGs) were recorded, and ventilator settings ( $V_T$ ,  $f$ ) were documented each time an ABG was drawn. No attempt was made to document the presence or absence of shivering activity.

Arterial carbon dioxide tension ( $P_{aCO_2}$ ) values were examined to assess the efficacy of mechanical ventilation in the ICU. Corrected  $P_{aCO_2}$  values that occurred outside the normal range (35–45 mm Hg) were noted on admission to the ICU and during rewarming.

Data were described as mean  $\pm$  SD. Increase in mean temperature between admission to the ICU and peak rewarming was analyzed by paired  $t$ -test. The relationship between age, BSA, and CPB data to the pattern of rewarming was studied by linear regression. The distribution of respiratory alkalosis and acidosis on admission to the ICU and during rewarming was analyzed by  $\chi^2$ , using the Yate's correction factor for small tables. A probability coefficient ( $P$  value) of  $< 0.05$  was taken to be statistically significant.

## Results

A total of 73 patients was studied; 46 men and 26 women. The mean age of the group was 60.5 yr, with

Table 1. Cardiopulmonary Bypass (CPB) Data

Duration of CPB	107.5 min	$\pm 43.2$
Cooling time on CPB	56.1 min	$\pm 30.7$
Warming time on CPB	51.6 min	$\pm 17.6$
Nadir NPT on CPB	29.5 °C	$\pm 1.7$
Zenith NPT on CPB	36.2 °C	$\pm 0.7$

All values are means  $\pm$  SD. NPT, nasopharyngeal temperature.

a range of 34–80 yr. The mean BSA of the group was 1.81 m<sup>2</sup>, with a range of 1.3–2.2 m<sup>2</sup>. Within the group, 43 patients had coronary artery bypass surgery, 21 had valvular surgery, and 9 had combined procedures. The time spent warming on CPB was equivalent to the time spent cooling (Table 1). Mean values for endpoints of cooling and warming on CPB were close to those predicted.

The pattern of increase in temperature after admission to the ICU has the appearance of a smooth sigmoid curve (Fig. 1). On the basis of mean rectal temperature, patients arrived in the ICU relatively cold ( $< 34.7 \pm 0.9^\circ\text{C}$ ). Rewarming commenced shortly and appeared to be most rapid 2–4 hr after admission to the ICU. Rewarming continued to a peak temperature of  $38.3 \pm 0.7^\circ\text{C}$  at  $8 \pm 2$  hr, after which it decreased towards normal. The difference in mean rectal temperature between admission and peak of rewarming was statistically significant.

On the basis of linear regression analysis, there was poor correlation ( $r < 0.3$ ) between the rapidity and degree of postoperative rewarming and any of the documented variables (age, BSA, duration of CPB, time of cooling and warming on CPB, and nadir and zenith nasopharyngeal temperature on CPB).

The incidence and distribution of abnormal  $P_{aCO_2}$  values observed on mechanical ventilation are detailed in Table 2. On admission, the most common acid-base abnormality was acute respiratory alkalosis, which occurred in 32% of patients. On the other hand, during rewarming, the most common abnormality was acute respiratory acidosis, which was observed in 42% of patients. These differences were statistically significant.

## Discussion

Approaches to temperature regulation during general anesthesia are predicated on the concept of a central body core—vital organs such as the brain and heart—within which temperature varies minimally, surrounded by peripheral tissues which interface with the environment through temperature gradients (4). Cardiac surgery produces profound hypothermic stress because on CPB, in addition to surface losses, the core

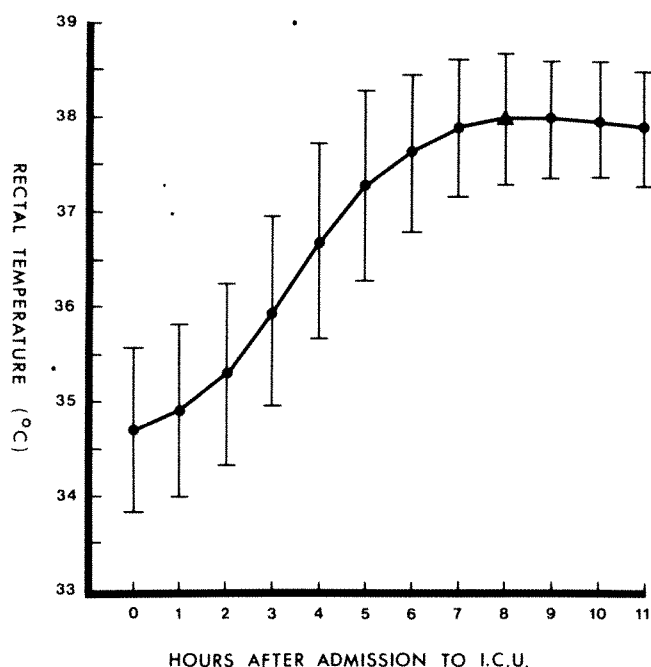


Figure 1. Rectal temperature after admission to the ICU. Patients are admitted to the ICU cold (mean 34.7°C) and rewarm to a mean of 38.3°C. Rewarming is completed by 8 hr after admission, but the most rapid rate of rewarming occurs 2–4 hr after admission. After 8 hr, temperature tends to settle back toward normal. Each point represents the mean rectal temperature  $\pm$  SD.

itself is rapidly cooled by heat exchange of the entire circulating blood volume.

The overall pattern of temperature changes we have observed during and after cardiac surgery is outlined in Figure 2. Nasopharyngeal temperature decreases rapidly to its nadir during cooling on CPB. At the end of warming on bypass, nasopharyngeal temperature is usually returned to near normal. However a decline in temperature, referred to as afterdrop, occurs over the next 90 min, so that by the time the patient is admitted to the ICU, nasopharyngeal temperature is substantially cooler. Although nasopharyngeal temperature was not measured in the ICU in this study, we subsequently have found no significant difference between it and rectal temperature when the patient is admitted to the ICU (5). The difference between nasopharyngeal temperature at the end of CPB (36.2°C) and rectal temperature on admission to the ICU (34.7°C) indicates the degree of afterdrop in this group of patients.

Harris et al. (6) pointed out the disparity between nasopharyngeal and muscle temperature on cardiopulmonary bypass, due to the temperature gradients that exist between vascular and less vascular parts of the body. Noback and Tinker (2) postulated that during hypothermic CPB, vasoconstriction akin to a state

Table 2.  $\text{PaCO}_2$ , pH, and Rewarming

	Admission to ICU	During rewarming
$\text{PaCO}_2 < 35$ mm Hg, pH $> 7.45$	23 (32%)	10 (14%)
$\text{PaCO}_2 > 45$ mm Hg, pH $< 7.35$	4 (5%)	31 (42%)

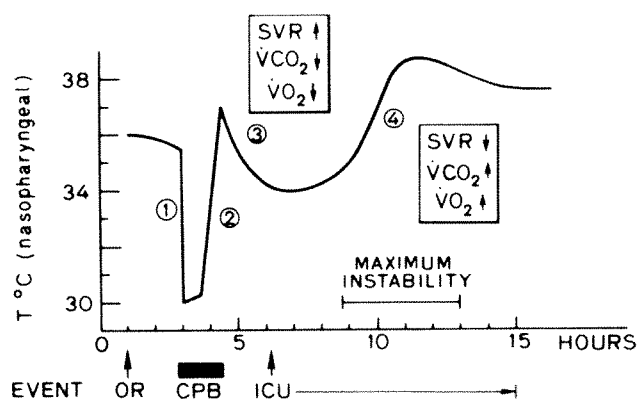
$\chi^2$ -analysis with Yate's correction  $P < 0.001$ .

of shock is induced. During warming on CPB, many constricted beds do not dilate and are insufficiently warmed, despite some minutes spent with nasopharyngeal temperature at 37°C. When these beds ultimately dilate (about 45 min after CPB) heat transfers to these beds from the warm core (i.e., blood) and nasopharyngeal temperature drops. This concept is supported by Stanley and Jackson (7), who found that the use of high flow (100 ml·kg<sup>-1</sup>·min<sup>-1</sup>) and mean arterial pressure (96 mm Hg) on CPB maintained muscle perfusion and prevented afterdrop. Niemenen et al. (8) found no difference in temperature gradients and afterdrop when either halothane or fentanyl were used after cardiac surgery, suggesting that anesthetic agents themselves do not play a primary role in this phenomenon. It appears that warming is usually not complete on CPB; large areas of the body such as muscle remain relatively cold, and afterdrop reflects a redistribution of heat from the warm core to the cold periphery. When patients enter the ICU they are still hypothermic.

The results of the present study demonstrate that the pattern of temperature change in the postoperative period after hypothermic cardiopulmonary bypass is consistent in a large number of patients. Mild hypothermia (34.7°C) on admission to the ICU is followed by rapid rewarming, with a slight overshoot (to 38.3°C) before stabilization at about 8 hr. It is of note that the temperature curve is sigmoid-shaped rather than linear, with a period of very rapid rewarming occurring about 2–4 hr after admission. Metabolic consequences of rewarming (vasodilatation, increased O<sub>2</sub> consumption, increased CO<sub>2</sub> production) ought to be most profound during this stage.

The pathogenesis of rapid postoperative rewarming is not well understood. In the present study, no predictable relationship was demonstrated between the pattern of rewarming and factors such as patient age and size, or the duration and extent of cooling and warming on CPB. Ross et al. (9) suggested that the rapid increase in central temperature is a result of the body's inability to lose heat due to surface vasoconstriction induced by the prior hypothermia, a concept reinforced by Molnar and Read (10). Another important factor may be the alteration of the body's





**Figure 2.** Nasopharyngeal temperature during and after cardiac surgery. (1) Core (i.e., blood) cooling on CPB. (2) Core warming on CPB. (3) Afterdrop in T after separation from CPB. (4) Rewarming after admission to ICU. Systemic vascular resistance (SVR) is increased, and  $\dot{V}\text{CO}_2$  and  $\dot{V}\text{O}_2$  are decreased on admission to the ICU because of residual hypothermia. During rapid rewarming SVR decreases and  $\dot{V}\text{CO}_2$  and  $\dot{V}\text{O}_2$  increase, which can cause marked cardiac and ventilatory instability. Symbols: T, temperature; OR, operating room; CPB, cardiopulmonary bypass; ICU, intensive care unit. (Reproduced, with permission, from Sladen RN. Management of the adult cardiac patient in the intensive care unit. In: Ream AK, Fogdall RP, eds. Acute cardiovascular management: anesthesia and intensive care. Philadelphia: Lippincott, 1982:495.)

normal homeothermic mechanisms by anesthetic agents. For example, narcotics such as fentanyl appear to "reset the thermostat" in the hypothalamic thermoregulatory center, whereas volatile anesthetic agents and vasodilators alter surface blood flow and interfere with peripheral feedback (8). It has been estimated that even after the mild hypothermia of general anesthesia, heat gain occurs at four to five times the rate of heat loss (11) and may occur even without obvious shivering (12).

Because the patients were all still anesthetized, they were entirely dependent on mechanical ventilatory support for adequate gas exchange. Abnormal  $\text{PaCO}_2$  values occur when the ventilator prescription (i.e., delivered minute ventilation) does not match changes in dead space or  $\text{CO}_2$  production.

On admission to the ICU, the most common error in prescription was hyperventilation. The most likely explanation is that in cold patients,  $\text{CO}_2$  production is relatively low, so minute ventilation requirement was overestimated. Acute respiratory alkalosis could exacerbate hypokalemia and ventricular irritability in the early postoperative period.

During rapid rewarming 2-5 hr after admission to the ICU, the most common error in prescription was hypoventilation. It is likely that as  $\text{CO}_2$  production increased, minute ventilation requirement was underestimated. Acute respiratory acidosis might compro-

mise myocardial performance at a time of rapid vasodilation and increased oxygen demand, and contribute to hemodynamic instability.

In conclusion, this study has demonstrated that rapid rewarming after hypothermic cardiopulmonary bypass is a consistent feature of the postoperative period and that it follows a sigmoid rather than linear pattern. However, the rate and degree of rewarming does not appear to be predictable on the basis of such factors as patient age and size, or warming time on CPB. Despite postoperative controlled mechanical ventilation, acid-base abnormalities due to an inappropriate ventilator prescription were commonly observed. Of these, the most striking was acute respiratory acidosis, which occurred in 42% of patients during rewarming. Further study is needed to clarify whether this process is due to changes in dead space or  $\text{CO}_2$  production, to identify the role of shivering, and to determine what measures would improve ventilatory management in the early postoperative period.

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## Review Article

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# One-Lung Ventilation and Hypoxic Pulmonary Vasoconstriction: Implications for Anesthetic Management

Jonathan L. Benumof, MD

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Thoracic surgery may be greatly facilitated by isolating one lung from the other, or by causing selective atelectasis of the lung being operated on (one-lung ventilation/anesthesia conditions), or both. Although blood flow to the nonventilated lung may be decreased by hypoxic pulmonary vasoconstriction (HPV), the nonventilated lung will still be perfused and therefore the arterial oxygen tension ( $\text{PaO}_2$ ) will decrease. Inhibition of nonventilated lung HPV by anesthetic drugs might further decrease  $\text{PaO}_2$  during one-lung ventilation. This review discusses the indications for one-lung ventilation, the determinants of blood flow distribution during one-lung ventilation, the effects of commonly used one-lung ventilation maneuvers on the one-lung ventilation blood flow distribution, and the effect of inhalational and intravenous anesthetic drugs on HPV. In this review it has been assumed that the method used to separate the two lungs has been correctly performed (e.g., the double-lumen tube is properly positioned). Final conclusions and clinical recommendations are based on the foregoing considerations.

### Indications for Isolation of the Two Lungs and/or One-Lung Ventilation

There are several absolute indications for isolating the two lungs from each other. Isolation of one lung from the other is absolutely necessary to prevent major

spillage or contamination from an infected (abscessed) or bleeding lung to the noninvolved lung. The presence of a large bronchopleural fistula, bronchopleural cutaneous fistula, or giant unilateral lung cyst requires the use of a double-lumen endotracheal tube in order to safely provide adequate ventilation to only the noninvolved side. One-lung anesthesia is absolutely necessary in order to perform unilateral bronchopulmonary lavage in patients with pulmonary alveolar proteinosis (and rarely, asthma and cystic fibrosis).

Isolation of the lungs from each other is indicated when collapse of one lung confers a critical benefit to the performance of surgery by facilitating surgical exposure. Thus pneumonectomy, upper lobectomy (technically the most difficult lobectomy), and repair of a thoracic aortic aneurysm may be made much easier by eliminating ventilation to the lung on the side of the procedure. In addition, examination of the pleural space (thoracoscopy) is considerably aided by collapse of the ipsilateral lung. Indications for the separation of the two lungs for some other surgical procedures, such as middle and lower lobectomies or esophageal resection are less firm. However, it should be remembered that collapse of the lung being operated on minimizes routine lung manipulation and avoids the occasional need for severe intraoperative retraction of the lung; severe lung retraction may further impair gas exchange intra- (1,2) and postoperatively (3,4). The separation of the lungs and use of differential lung ventilation is occasionally indicated following removal of totally occluding and predominantly unilateral chronic pulmonary emboli (postcardiopulmonary bypass), due to transudation of fluid across the alveolar capillary membrane in the region of the lung supplied by the previously occluded vessel (reperfusion of a previously nonperfused vascular bed).

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## Blood Flow Distribution During One-Lung Ventilation

Anesthesia for thoracic surgery is most commonly performed with the patient in the lateral decubitus position with the nondependent hemithorax comprising the operative field. When one-lung ventilation is employed, the nondependent lung is the nonventilated and collapsed (atelectatic) lung, and the dependent lung is the ventilated lung. Consequently, one-lung ventilation creates an obligatory right-to-left transpulmonary shunt through the nonventilated nondependent lung that is not present during two-lung ventilation. Thus it is not surprising to find that, given the same inspired oxygen concentration ( $F_iO_2$ ) and hemodynamic and metabolic status, one-lung ventilation results in a much larger alveolar-to-arterial oxygen tension difference and lower arterial oxygen tension ( $PaO_2$ ) than does two-lung ventilation (5). Fortunately, there are both passive mechanical and active vasomotor mechanisms that are usually operant that minimize the blood flow to the nondependent nonventilated lung and thereby prevent the  $PaO_2$  from decreasing as much as might be expected from a two-lung ventilation blood flow distribution basis.

### Blood Flow to the Nondependent Nonventilated Lung

The passive mechanical mechanisms consist of gravity and surgical interference with blood flow. Gravity causes a vertical gradient in the distribution of pulmonary blood flow in the lateral decubitus position for the same reason that it does in the upright position. Consequently, blood flow to the nondependent lung is less than blood flow to the dependent lung. The gravity component of blood flow reduction to the nondependent lung should be constant with respect to both time and magnitude. Severe surgical compression (directly compressing lung vessels) and retraction (causing kinking and tortuosity of lung vessels) of the nondependent lung may further passively reduce nondependent lung blood flow. In addition, ligation of pulmonary vessels for pulmonary resection will greatly decrease nondependent lung blood flow. The surgical interference component of blood flow reduction to the nondependent lung should be variable with respect to both time and magnitude.

The most significant reduction in blood flow to the nondependent lung is caused by an active vasoconstrictor mechanism. The normal response of the pulmonary vasculature to atelectasis is an increase in pulmonary vascular resistance (PVR) (in just the atelectatic lung), and the increase in atelectatic lung PVR

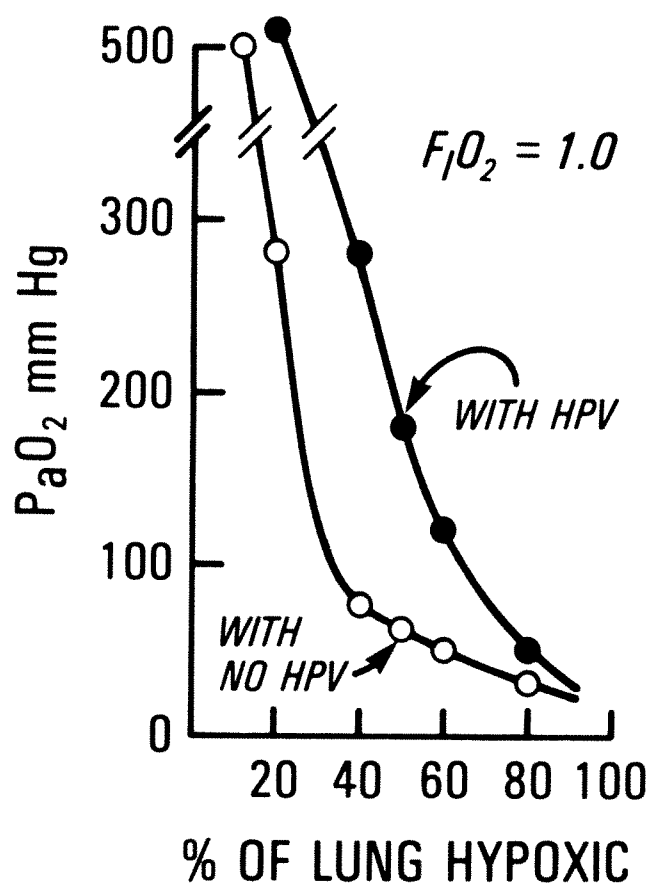


Figure 1. Effect of HPV on  $PaO_2$ . HPV, hypoxic pulmonary vasoconstriction. As the percent of lung that is hypoxic is increased (x axis), the arterial  $PO_2$  ( $PaO_2$ ) decreases (y axis). When the amount of lung that is hypoxic is 30–70%, which is in the one-lung ventilation/anesthesia range, the decrease in  $PaO_2$  is much greater when there is no HPV compared to when there is the normal expected amount of HPV (10).

is thought to be due almost entirely to HPV (6,7). This conclusion applies whether ventilation is spontaneous or with positive pressure, and whether the chest is open or closed (8). It is possible that a slight amount of further subacute (greater than 30 min) decrease in blood flow to atelectatic lung is due to mechanical effects of atelectasis on lung blood vessels (9).

The selective increase in atelectatic lung PVR diverts blood flow away from the atelectatic lung towards the remaining normoxic or hyperoxic ventilated lung. The diversion of blood flow minimizes the amount of shunt flow that occurs through hypoxic lung. Figure 1 shows the theoretically expected effect of HPV on arterial oxygen tension ( $PaO_2$ ) as the amount of lung that is made hypoxic increases (10). When very little of the lung is hypoxic (near 0%) it does not matter, in terms of  $PaO_2$ , whether the small amount of lung has HPV or not because in either case the shunt will be small. When most of the lung is hypoxic (near



100%) there is no significant normoxic region for the hypoxic region to divert flow to, and again it does not matter, in terms of  $\text{PaO}_2$ , whether the hypoxic region has HPV or not. When the percentage of lung that is hypoxic is intermediate (between 30–70%), which is the amount of lung that is hypoxic during the one-lung ventilation/anesthesia condition, there is a large difference between the  $\text{PaO}_2$  expected with a normal amount of HPV (10) compared to when there is no HPV. In fact, in this range of hypoxic lung, HPV can increase  $\text{PaO}_2$  from levels that might cause arrhythmias to much higher and safer values. It is not surprising then, that numerous clinical one-lung ventilation studies (5,11–19) have found that the shunt through the nonventilated lung is usually 20–25% of the cardiac output as opposed to the 40–50% shunt that might be expected if there was no HPV in the nonventilated lung. Thus HPV is an autoregulatory mechanism that protects the  $\text{PaO}_2$  by decreasing the amount of shunt flow that can occur through the hypoxic lung.

The amount of disease in the nondependent lung should also be a significant determinant of the amount of blood flow to the nondependent lung. If the nondependent lung is severely diseased, then there may be a fixed reduction in blood flow to this lung preoperatively, and collapse of such a diseased lung may not cause an increase in shunt. Thus it is not surprising that administration of sodium nitroprusside and nitroglycerin to chronic obstructive pulmonary disease patients, who have a fixed reduced cross-sectional area of the pulmonary vascular bed, does not cause an increase in shunt (20) as it does in patients with normal lungs (21). If the nondependent lung is normal and has a normal amount of blood flow, then collapse of such a normal lung may be associated with a higher nonventilated nondependent lung blood flow and shunt. A higher one-lung ventilation shunt through the nondependent lung is much more likely to occur in patients who require thoracotomy for nonpulmonary disease (16). However, the above theoretical relationship between the amount of nondependent lung disease and shunt during one-lung ventilation has not been systematically studied to the author's knowledge.

There are numerous other significant factors that may affect the amount of nondependent lung HPV (see, in particular, Effect of Anesthetics section below). Most systematic vasodilator drugs inhibit regional HPV. Those specifically studied have been nitroglycerin (21), nitroprusside (21), dobutamine (22,23), several calcium antagonists (24–28), and many  $\beta_2$ -agonists (isoproterenol, ritodrine, orciprenaline, salbutamol, ATP, and glucagon) (23,29–32). Aminophylline and hydralazine may not decrease HPV (33,34).

Vasoconstrictor drugs (dopamine, epinephrine, phenylephrine) seem to preferentially constrict normoxic lung vessels, thereby disproportionately increasing normoxic lung pulmonary vascular resistance (22,23,32,35). The increase in normoxic lung vascular resistance will decrease normoxic lung blood flow and increase atelectatic lung blood flow. The effect of vasoconstrictor drugs is similar to decreasing normoxic lung  $\text{FI}_{\text{O}_2}$  (see below).

The HPV response is maximal when pulmonary vascular pressure is normal and is decreased by either high or low pulmonary vascular pressure. The mechanism for high pulmonary vascular pressure inhibition of HPV is simple; the pulmonary circulation is poorly endowed with smooth muscle and cannot constrict against an increased vascular pressure (36,37). The mechanism for low pulmonary vascular pressure inhibition of HPV is more complex. In order for this to occur, the hypoxic compartment must be atelectatic; under these circumstances, when pulmonary vascular pressure decreases it is now possible for part of the ventilated lung (but not the atelectatic lung) to be in a zone 1 condition (alveolar pressure increases relative to pulmonary artery pressure) and experience a disproportionate increase in pulmonary vascular resistance that would divert blood flow back over to the atelectatic lung, thereby inhibiting atelectatic lung HPV (38).

The HPV response is also maximal when the mixed venous oxygen tension ( $\text{PvO}_2$ ) is normal, and is decreased by either high or low  $\text{PvO}_2$ . The mechanism for high  $\text{PvO}_2$  inhibition of HPV is presumably due to reverse diffusion of oxygen, causing the oxygen tension of either the vessels, interstitial or alveolar spaces, or all of these to be increased above the HPV threshold (39). That is, if enough oxygen can get to some receptor in the small arteriole–capillary–alveolar area, then the vessels will not vasoconstrict. The mechanism for low  $\text{PvO}_2$  inhibition of HPV is due to the low  $\text{PvO}_2$  decreasing alveolar oxygen tension in the normoxic compartment down to a level sufficient to induce HPV in the supposedly “normoxic” lung (40). The HPV in the “normoxic” lung competes against and offsets the HPV in the originally hypoxic lung and results in no blood flow diversion away from the more obviously hypoxic lung.

Hypocapnia has been thought to directly inhibit regional HPV, and hypercapnia to directly enhance regional HPV (36,41). In addition, during one-lung ventilation conditions, hypocapnia can only be produced by hyperventilation of the one lung. The hyperventilation requires an increased ventilated lung airway pressure which causes increased ventilated lung pulmonary vascular resistance, which in turn diverts

blood flow back into the hypoxic lung. Hypercapnia during one-lung ventilation seems to act as a vasoconstrictor drug by selectively increasing ventilated lung pulmonary vascular resistance.

The effects of changes in airway pressure due to end-expiratory pressure and tidal volume changes will be discussed in detail below. There is some evidence that certain types of infections (which may cause atelectasis), particularly granulomatous and pneumococcal infections, may inhibit HPV (42,43).

### *Blood Flow to the Dependent Ventilated Lung*

The dependent lung usually has an increased amount of blood flow due to both passive gravitational effects and active nondependent lung vasoconstrictor effects. However, the dependent lung may also have an hypoxic compartment (areas of low ventilation to perfusion ratio and atelectasis) that was present preoperatively or developed intraoperatively. The dependent lung hypoxic compartment may develop intraoperatively for several reasons. First, in the lateral decubitus position, the ventilated dependent lung usually has a reduced lung volume due to the combined factors of induction of general anesthesia and circumferential (and perhaps severe) compression by the mediastinum from above, by the abdominal contents pressing against the diaphragm from the caudad side, and by suboptimal positioning effects (rolls, packs, shoulder supports) pushing in from the dependent side and axilla (Fig. 2, upper left panel) (44-47). Second, absorption atelectasis can also occur in regions of the dependent lung that have low ventilation/perfusion ratios when they are exposed to high inspired oxygen concentration (48,49). Third, difficulty in secretion removal may also cause the development of poorly ventilated and atelectatic areas in the dependent lung. Finally, maintaining the lateral decubitus position for prolonged periods of time may cause fluid to transudate into the dependent lung (which may be vertically below the left atrium), and cause further decreased lung volume and increased airway closure in the dependent lung (50). A decrease in lung volume and an increase in airway closure in the dependent lung will create areas that have a low ventilation/perfusion ratio or atelectasis (48).

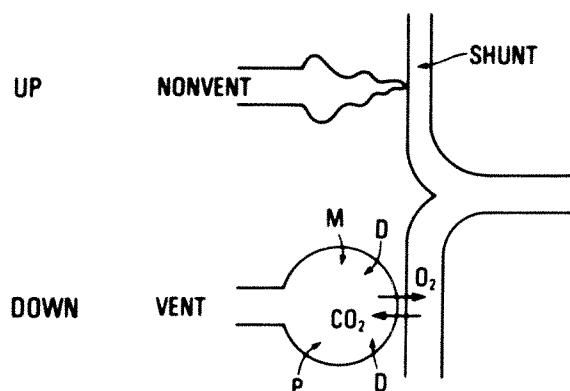
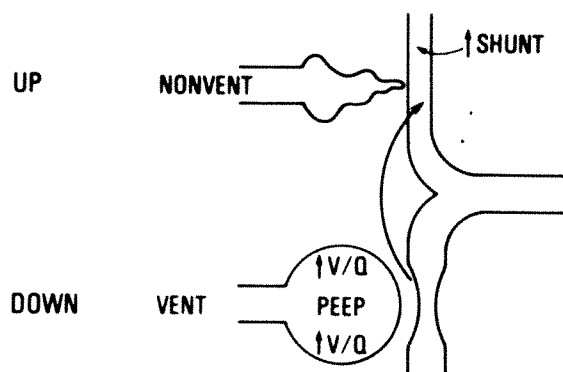
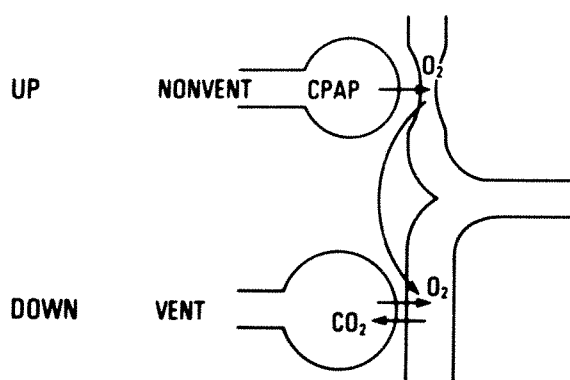
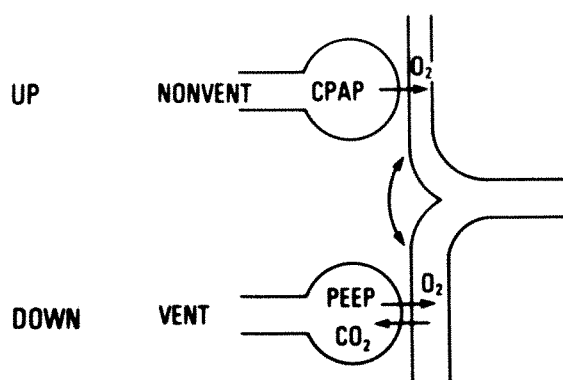
The development of low ventilation/perfusion ratio and/or atelectatic areas in the dependent lung will increase vascular resistance in the dependent lung (45,51) (due to dependent lung HPV) (52), thereby decreasing dependent lung blood flow and increasing nondependent lung blood flow (53). Stated differently, the pulmonary vascular resistance in the ventilated compartment of the lung determines the ability

of the ventilated, and supposedly normoxic, lung to accept redistributed blood flow from the hypoxic lung. Clinical conditions that are independent of specific dependent lung disease, but which may still increase dependent lung vascular resistance in a dose-dependent manner, are a decreasing inspired oxygen tension in the dependent lung (from 1.0 to 0.5-0.3) (37,53,54) and a decreasing temperature (from 40-30°C) (55).

### *Effect of One-Lung Ventilation Maneuvers on the Nondependent/Dependent Lung Blood Flow Distribution*

Various commonly used one-lung ventilatory maneuvers may significantly change the partitioning of blood flow between the nondependent and dependent lungs.

*Conventional management of one-lung ventilation.* The proper initial conventional management of one-lung ventilation is logically based on the above one-lung ventilation pathophysiologic considerations. First, although the theoretical possibilities of absorption atelectasis and oxygen toxicity exist, the benefits of ventilating the dependent lung with 100% oxygen far exceed the risks. A high  $FiO_2$  in the single ventilated lung may critically increase the  $PaO_2$  from arrhythmogenic and life-threatening levels to safer levels. In addition, a high  $FiO_2$  in the dependent lung will vasodilate the dependent lung, thereby increasing the dependent lung capability of accepting blood flow redistribution due to nondependent lung HPV (37,53). Direct chemical 100% oxygen toxicity will not occur during the operative period (56) and absorption atelectasis in the dependent lung (49) is unlikely to occur in view of the remaining one-lung ventilation management characteristics listed below. Second, the dependent lung should be ventilated with a tidal volume of 10 ml/kg. Use of a tidal volume less than 10 ml/kg might promote dependent lung atelectasis. Use of a tidal volume greater than 10 ml/kg might excessively increase dependent lung airway pressure and vascular resistance (51), and thereby increase nondependent lung blood flow (decrease nondependent lung HPV) (57-59). Third, the respiratory rate should be set so that the  $PaCO_2$  remains at 40 mm Hg (usually requires a 20% increase above the rate used for two-lung ventilation). Hypocapnia should be avoided because use of the airway pressure in the dependent lung necessary to produce systemic hypocapnia may excessively increase dependent lung vascular resistance. Furthermore, hypocapnia may directly inhibit HPV in the nondependent lung (36,42). Finally, none

**ONE LUNG VENTILATION: THE SITUATION****ONE LUNG VENTILATION: DOWN LUNG PEEP****ONE LUNG VENTILATION: UP LUNG CPAP****ONE LUNG VENTILATION: DIFFERENTIAL LUNG CPAP/PEEP**

or just a very low level of dependent lung PEEP (less than 5 cm H<sub>2</sub>O) should be used initially because of concern of unnecessarily increasing dependent lung vascular resistance (see selective dependent lung PEEP section below).

Very occasional ventilation of the nondependent lung (one breath every 5–10 min) causes some oxygen or oxygen-enriched gas to remain in the nonventilated lung, and blood flowing through this lung can continue to take up some oxygen for a period of some minutes. Of course the effect of an occasional positive pressure breath to the nondependent lung on arterial oxygenation will be uncertain with regard to magnitude and temporal profile, and requires the nondependent lung to be incompletely collapsed for a period of some minutes.

*Selective dependent lung PEEP.* Since the ventilated lung often has a decreased lung volume during one-

Figure 2. The figure is a four part schematic diagram showing the effects of various differential lung management approaches. The one-lung ventilation situation is depicted in the upper left-hand panel. The DOWN (dependent) lung is ventilated (VENT), but is compressed by the weight of the mediastinum (M) from above, the pressure of the abdominal contents against the diaphragm (D), and by positioning effects of rolls, packs, and shoulder supports (P). The UP (nondependent) lung is nonventilated (NONVENT), and blood flow through this lung is shunt flow. In the upper right-hand panel, the dependent lung has been selectively treated with PEEP, which improves ventilation to perfusion (V/Q) relationships in the dependent lung but also increases dependent lung vascular resistance; this diverts blood to, and thereby increases shunt flow through, the nonventilated lung. In the lower left-hand panel, selective application of CPAP to the nondependent lung permits oxygen uptake from this lung; even if the CPAP causes an increase in vascular resistance and diverts blood flow to the dependent lung, the diverted blood flow can still participate in gas exchange in the ventilated dependent lung. Consequently, selective nondependent lung CPAP can greatly increase PaO<sub>2</sub>. With differential lung CPAP (nondependent lung)/PEEP (dependent lung) (lower right-hand panel) it does not matter where the blood flow goes since both lungs can participate in O<sub>2</sub> uptake. With this latter one-lung ventilation pattern, PaO<sub>2</sub> can be restored to levels that are near those achieved by two-lung ventilation.

lung ventilation, it is not surprising that several attempts have been made to improve oxygenation by treating the ventilated lung with PEEP (15,19,57-61). However, the selective application of PEEP to the ventilated lung has had variable and directionally opposite (both good and bad) effects on oxygenation. The most accepted mechanism by which PEEP is thought to be of benefit is that PEEP causes an increase in lung volume at end-expiration (by definition, the functional residual capacity (FRC)). The increase in FRC contributes to the prevention of airway and alveolar closure at end-expiration and to the recruitment of airways and alveoli during inspiration. The increases in lung volume and airway and alveolar openings result in increases in lung compliance, ventilation, and the ratio of ventilation-to-perfusion of the single ventilated lung (Fig. 2, upper right panel) (47,62).

An accepted risk of PEEP is that the PEEP-induced increase in lung volume can cause compression of the small intraalveolar vessels. If the PEEP-induced intraalveolar vessel compression is geographically widespread (i.e., two-lung ventilation), then total pulmonary vascular resistance increases and cardiac output decreases. If the intraalveolar vessel compression is limited to just the one ventilated lung, then pulmonary vascular resistance of the ventilated and PEEPed lung increases, which causes diversion of blood flow away from the ventilated lung to the nonventilated lung (Fig. 2, upper right panel) (57,59). Thus the various one-lung ventilation-PEEP studies have had patients who have had an increase (19,58), no change (58,60,63), or a decrease (19,58,61) in oxygenation. The additive effects of increases in PEEP and tidal volume in the ventilated lung in decreasing  $\text{PaO}_2$  in animals further confirms the one ventilated lung volume vs vascular resistance hypothesis (58). Although in none of these studies was a dose (ventilated lung PEEP)-response ( $\text{PaO}_2$ ,  $\dot{Q}_s/\dot{Q}_t$  value) relationship described, it seems reasonable to postulate on the basis of these results that the therapeutic margin of ventilated lung PEEP is quite narrow. Other studies have shown that high tidal volumes (15), variations in the inspiratory-to-expiratory ratio (63), and intermittent manual hyperventilation of the lower lung are not beneficial (63).

*Selective nondependent lung CPAP.* PEEP can be selectively applied to just the nonventilated (up) lung. Since under these conditions the nonventilated lung is only slightly but constantly distended by oxygen, a better term for this ventilatory pattern arrangement would be nonventilated lung continuous positive airway pressure (CPAP). Recently, two reports, one in

humans (61) and one in dogs (64), have shown that the application of CPAP (without tidal ventilation) to only the nonventilated lung significantly increased oxygenation. The latter study was performed with the dogs in the lateral decubitus position and showed that low levels of CPAP (5-10 cm  $\text{H}_2\text{O}$ ) to the nonventilated nondependent lung increased  $\text{PaO}_2$  and decreased shunt, although blood flow to the nonventilated lung remained unchanged. Therefore, low levels of CPAP simply maintained the patency of nondependent lung airways allowing some oxygen distention of the gas exchanging alveolar space in the nondependent lung (Fig. 2, lower left panel). On the other hand, 15 cm  $\text{H}_2\text{O}$  of CPAP caused similar  $\text{PaO}_2$  and shunt changes while blood flow to the nonventilated nondependent lung decreased significantly. Therefore, high levels of nonventilated lung CPAP act by permitting oxygen uptake in the nonventilated lung, as well as by causing blood flow diversion to the ventilated lung where both oxygen and carbon dioxide exchange can take place (Fig. 2, lower left panel). Because low levels of nonventilated lung CPAP are as efficacious as high levels of nonventilated lung CPAP, and have less surgical interference and hemodynamic implications, it is logical to first use low levels of nonventilated CPAP. In my experience, low levels of nonventilated CPAP have corrected severe hypoxemia ( $\text{PaO}_2 < 50$  mm Hg) more than 90% of the time, provided the double-lumen tube was correctly positioned. In both the human (61) and dog studies (64), oxygen insufflation at zero airway pressure did not significantly improve  $\text{PaO}_2$  and shunt, and this result was probably due to the inability of zero transbronchial airway pressure to maintain airway patency. Several easy to assemble selective nondependent lung CPAP systems have been recently described (61,65,66).

*Differential lung PEEP, CPAP.* In theory, and from the above considerations, it seems that the best treatment or way to improve oxygen during one-lung ventilation is the application of differential lung PEEP or PEEP/CPAP. In this situation, the ventilated lung is PEEPed in the usual conventional manner in an effort to improve ventilated lung volume and ventilation-to-perfusion relationships. Simultaneously, the nonventilated lung receives CPAP in an attempt to improve oxygenation of the blood perfusing the nonventilated lung. Therefore, with differential lung PEEP or PEEP/CPAP, it does not matter where the blood flow goes nearly as much as during simple one-lung ventilation, because wherever it goes (either ventilated or nonventilated lung) it has at least some chance to participate in gas exchange with alveoli that are



expanded with oxygen (Fig. 2, lower right panel). In support of this contention, oxygenation has been increased significantly in patients during thoracotomy in the lateral decubitus position (utilizing two-lung ventilation) when PEEP has been added to the ventilated dependent lung, while the nondependent lung was also able to participate in gas exchange by virtue of being ventilated at zero end-expiratory pressure (ZEEP) (47).

In fact, there are now multiple reports of significant increases in oxygenation obtained with the application of differential lung ventilation and positive end-expiratory pressure (either PEEP/PEEP, PEEP/CPAP, or CPAP/CPAP) through double-lumen tubes to patients in the intensive care unit with acute respiratory failure due to predominantly unilateral lung disease (67-75). In all cases conventional whole lung therapy (mechanical ventilation, PEEP, CPAP) administered via a standard single-lumen tube either failed to improve or actually decreased oxygenation. In most cases the amount of PEEP initially administered to each lung was inversely proportional to the compliance of each lung; presumably and ideally this PEEP arrangement should result in equal FRC in each lung. In some cases, the amount of each lung PEEP was later readjusted and titrated in an effort to find a differential lung PEEP combination that resulted in the lowest right-to-left transpulmonary shunt. The present state of the art with differential lung PEEP and tidal ventilation has advanced to the point where special equipment has been developed to facilitate the application of this form of respiratory therapy (61,70,76,77).

### Effect of Anesthetics on Hypoxic Pulmonary Vasoconstriction

General anesthesia with controlled ventilation is the safest method of anesthetizing patients for the vast majority of elective thoracic procedures. While a variety of general anesthesia techniques can be used, the volatile halogenated anesthetic drugs are good choices for several reasons. First, the halogenated drugs have a salutary effect on airway irritability; the mechanism of this action is controversial but there is evidence that these drugs can block specific forms of bronchoconstriction (78,79), as well as have a non-specific bronchodilating effect related to the depth of anesthesia (80). Obtundation of airway reflexes in patients who have reactive airways (i.e., smokers), and who may have their airways directly manipulated by the surgeon is a highly desirable property of the general anesthesia produced by these drugs. Second, the use of volatile halogenated drugs allows delivery of

a high inspired oxygen concentration without loss of anesthesia. Although nitrous oxide/oxygen/narcotic/relaxant anesthesia technique can be used (81), nitrous oxide necessitates a significant decrease in the inspired oxygen concentration and increases the chance of developing hypoxemia (especially if one-lung ventilation is employed) (82). Third, since the volatile halogenated drugs can be rapidly eliminated, concern over postoperative hypoventilation in extubated patients may be diminished. Doses of intravenous anesthetics, such as the narcotics, ketamine, and the barbiturates, which render the patient areflexic to surgical stimulation, may cause the patient to require a period of postoperative ventilation. Fourth, in the usual clinical doses (near 1 MAC), the halogenated anesthetic drugs provide a reasonable degree of cardiovascular stability. This may be of particular importance in patients with coronary artery disease and systemic hypertension. Fifth, the halogenated drugs do not appear to decrease  $\text{PaO}_2$  any more than intravenous anesthetics during one-lung ventilation (see below) (13,83).

As theorized above, an undesirable property of general anesthesia would be inhibition of HPV in the nonventilated lung by the anesthetic drug. All of the inhalation and many of the injectable anesthetics have been studied with regard to effect on HPV. Halothane has been most extensively studied (Table 1) (7,84-99). The experimental preparations utilized may be divided into four basic categories: *in vitro*; *in vivo*-not intact (pumped perfused lungs, no systemic circulation or neural function); *in vivo*-intact (normally perfused lungs, normal systemic circulation); humans (volunteers or patients). It appears, according to this experimental preparation breakdown, that inhibition of HPV by halothane is a universal finding in the *in vitro* and *in vivo*-intact preparations. However, in the more normal or physiological *in vivo*-intact and human studies halothane has caused none, or only a very slight decrease, in HPV response. Thus it appears that a fundamental property of halothane is to inhibit HPV in experimental preparations which can be controlled for other physiological influences (i.e., pulmonary vascular pressure, cardiac output,  $\text{CO}_2$  level, temperature, etc.) on the HPV response, and in the more biologically complex *in vivo* models, other factors seem to be involved that greatly diminish the inhibitory effect of halothane on HPV. Important methodological differences between the *in vitro* and *in vivo*-not intact preparations and *in vivo*-intact and human models that could account for the observed differences in halothane effect on HPV are presence (or absence) of perfusion pulsations, perfusion fluid composition, size of perfusion circuit (96), baro-

Table 1. Effect of Halothane on Hypoxic Pulmonary Vasoconstriction (HPV) in Various Experimental Preparations

Anesthetic drug	Experimental preparation	Species	Regional (R) vs whole (W) lung hypoxia	Dose (converted to MAC)	Effect on HPV/magnitude of change <sup>a</sup>	Reference
Halothane	In vitro					
	vessel strips	Rabbit	W	1.2-2.4	↓/DR-TO ?	84
	heart-lung	Rat	W	1.3-2.1	↓/DR-TO 100%	85
	heart-lung	Rat	W	1-3	↓/DR-TO 100%	86
	heart-lung	Rat	W	2	↓/100%	87
	heart-lung	Rat	W	0-2	↓/DR-TO 90%	88
	heart-lung	Rat	W	2-4	↓/DR-TO 90%	7
	lung	Cat	W	0.5-2.5	↓/DR-TO 95%	89
	In vivo-not intact,	Cat	W	0.5	↓/50%	90
	pump perfused	Cat	W	1-3	↓/DR-TO 60%	91
	In vivo-intact,	Dog	W	1.5	↑/MODERATE	92
	normally perfused	Dog	W	0.5-1	SLIGHT HPV/SLIGHT ↓	93
		Dog	R	TO 1.7	↓ SLIGHT	94
		Dog	R	1	↓ SLIGHT	95
		Dog	R	0.5-1.5	0	96
		Dog	R	1-3	SLIGHT ↑ OR 0	97
		Dog	R	0-2	↓ SLIGHT	98
	Human	Human	R	0.5-2.0	↓/20-30% ?	99

<sup>a</sup>Abbreviations: ↓, decrease; ↑, increase; DR-TO %, HPV was progressively decreased to the maximum shown in column 6 over the concentration range shown in column 5.

receptor influences, absence of bronchial blood flow (which abolishes all central and autonomic nervous activity in the lung) (100), chemical influences (i.e., pH, PO<sub>2</sub>), humoral influences (i.e., histamine and prostaglandin release from body tissues), lymph flow influences, and, very importantly, the use of different species (101-103).

Ether has been the next most studied drug, and it appears that the quantitative effect of ether on HPV is also dependent on the type of experimental preparation used. Thus the in vitro and in vivo-not intact models show much more inhibition of HPV by anesthetic drug than the in vivo-intact and human models (Table 2) (7,85,86,89,91,104,105). Although the number of studies involving halogenated drugs other than halothane (isoflurane (88,97,98,106), enflurane (7,88, 107,108), methoxyflurane (84-86,109,110), fluroxene (97,98), and trichlorethylene (89)) have been too small to permit recognition of an experimental preparation result pattern, most of these anesthetics have demonstrated inhibition of HPV (at least in the in vitro models) (Table 2). Nitrous oxide seems to cause a small, somewhat consistent inhibition of HPV (Table 2) (86,93,97,98,111,112). All injectable anesthetics studied to date have no effect on HPV (Table 2) (85,86,94,97,108,113-115).

To summarize previous animal studies, it appears that a fundamental property of inhalational anesthetics is to decrease HPV. However, in intact animal preparations some biologic or physiologic property seems to remove or greatly lessen the inhibitory effect

of anesthetic drugs on HPV. It may be that the differences in effects of anesthetic drugs on regional HPV from preparation to preparation, anesthetic to anesthetic, and species to species (see below) are closely related to the mechanism of HPV, which is still unknown. A frequent extrapolation of the much more numerous in vitro and in vivo-not intact HPV studies is that anesthetic drugs might impair arterial oxygenation during one-lung anesthesia by inhibition HPV in the nonventilated lung.

Recently halothane and isoflurane have been specifically tested for effect on arterial oxygenation during one-lung ventilation in patients undergoing thoracotomy (13,83). In one study (13), stable one-lung ventilation conditions in the lateral decubitus position were established in patients who were anesthetized with only intravenous drugs. While stable one-lung ventilation was maintained, inhalational anesthetics were administered (halothane and isoflurane end-tidal concentrations were greater than 1 MAC for at least 15 min), and then discontinued (halothane and isoflurane end-tidal concentrations decreased to near zero). In the other study (83) steady-state one-lung ventilation conditions in the lateral decubitus position were established in patients who were anesthetized with only inhalational drugs (halothane and isoflurane end-tidal concentrations were constantly greater than 1 MAC for more than 40 min). While one-lung ventilation was continued, inhalational anesthesia was discontinued, and intravenous anesthesia administered (halothane and isoflurane end-tidal concentra-

**Table 2.** Effect of Ether, Isoflurane, Enflurane, Methoxyflurane, Fluroxene, Trichlorethylene, Nitrous Oxide and Injectable Anesthetics on Hypoxic Pulmonary Vasoconstriction (HPV)

Anesthetic drug	Experimental preparation	Species	Regional (R) vs whole (W) lung hypoxia	Dose (converted to MAC)	Effect on HPV/magnitude of change <sup>a</sup>	Reference
Ether	In vitro					
	heart-lung	Rat	W	0.5-1.0	↓ /DR-TO 100%	85
	heart-lung	Rat	W	1-2	↓ /DR-TO 100%	86
	heart-lung	Rat	W	4-6	↓ 60 + 70%	7
	lung	Cat	W	0.5-5.0	↓ 90 - 95%	89
	lung	Cat	W	1	↓ 85%	104
	In vivo-not intact, pump perfused	Cat	W	2.5-5.0	↓ /DR-TO 95%	91
	In vivo-intact, normally perfused	Dog	R	1.5-3.0	↓ /55%	105
	Human	Human	R	1-2	↓ /33%	99
Isoflurane	In vitro					
	heart-lung	Rat	W	0.2	↓ /DR-TO 90%	88
	In vivo-intact, normally perfused	Dog	R	1-3	↓ /DR-TO 60%	97
		Dog	R	1-2	↓ /DR-TO 50%	98
Enflurane		Dog	R	1-2	0	106
	In vitro					
	heart-lung	Rat	W	0-2	↓ /DR-TO 90%	88
	heart-lung	Rat	W	1-3	↓ /60%	7
Methoxyflurane	heart-lung	Rat	W	1-3	↓ /DR-TO 100%	107
	In vitro					
	vessel strips	Rabbit	W	1-5	Variable	84
	heart-lung	Rat	W	0.3-0.5	↓ /DR-TO 100%	85
Fluroxene	heart-lung	Rat	W	0.3-1.3	↓ /DR-TO 50%	86
	lung	Cat	W	1-10	↓ /DR-TO 100%	109
	In vivo-intact, normally perfused	Dog	R	3	0	110
	In vivo-intact, normally perfused	Dog	R	1-3	↓ /DR-TO 80%	97
Trichlorethylene						
	In vivo-intact, normally perfused	Dog	R	1-2	↓ /DR-TO 55%	98
N <sub>2</sub> O	In vitro					
	lung	Cat	W	0.5-2.5	↓ /DR-TO 90%	89
Injectable anesthetics	In vitro					
	heart-lung	Rat	W	1.4	0	86
	heart-lung	Rat	W	0.1-0.3	↓ /DR-TO 50%	111
	In vivo-not intact, pump perfused	Cat	W			
	In vivo-intact, normally perfused	Dog	W	0.3	↑ /Moderate	93
		Dog	R	0.6	↓ /30%	97
Injectable anesthetics		Dog	R	0.3	↓ /10%	98
		Dog	R	0.5	↓ /40%	112
	In vitro					
	heart-lung	Rat	W	Drugs used in these experiments were fentanyl, meperidine, morphine, thiopental, pentobarbital, hexobarbital, doperidol, diazepam, chlorpromazine, ketamine, pentazocine, lidocaine, buprenorphine. For doses and blood levels see references in far right column.	0	86
	heart-lung	Rat	W		0	85
	heart-lung	Rat	W		0	113
	In vivo-not intact, pump perfused	Cat	W		0	114
	In vivo-intact, normally perfused	Dog	R		0	114
		Dog	R		0	94
		Dog	R		0	97
	Humans	Humans	R		0	115

<sup>a</sup>Abbreviations: ↓, decrease; ↑, increase; DR-TO %, HPV was progressively decreased to the maximum shown in column 6 over the concentration range shown in column 5.

tions decreased to near zero). There was no significant difference in  $\text{PaO}_2$  during inhalation anesthesia with either halothane or isoflurane compared to intravenous anesthesia during one-lung ventilation in either of the two experimental sequences. Thus irrespective of whether inhalational anesthesia is administered before or after intravenous anesthesia during one-lung ventilation, inhalation anesthesia does not further impair arterial oxygenation. These findings are consistent with the interpretation that halothane and isoflurane do not significantly inhibit HPV in patients during one-lung ventilation in the lateral decubitus position.

## Conclusions and Clinical Recommendations

This review supports two conclusions. First, the studies of selective up lung CPAP (61,64) and differential lung PEEP (67-75), suggest that the sequence of treating hypoxemia during one-lung ventilation in the lateral decubitus position (simple tidal volume and respiratory rate adjustments should be made first, if appropriate) should be to apply 5-10 cm  $\text{H}_2\text{O}$  of CPAP cautiously to the nonventilated nondependent lung. Nondependent lung CPAP should be applied during the deflation phase of a large tidal volume breath in order to overcome critical opening pressures in the atelectatic lung. If oxygenation does not improve (which would be unusual), 5-10 cm  $\text{H}_2\text{O}$  of PEEP to the ventilated dependent lung should then be applied. If this does not improve oxygenation, dependent lung PEEP should be increased to 10-15 cm  $\text{H}_2\text{O}$  of PEEP while the nondependent lung is maintained at 5-10 cm  $\text{H}_2\text{O}$  of CPAP. In this way a differential lung CPAP/PEEP search for the maximum compliance and a minimum right-to-left transpulmonary shunt might be started, in an attempt to find the optimal end-expiratory pressure for each lung and the patient as a whole. In view of the efficacy of nonventilated CPAP, use of differential lung PEEP/CPAP should rarely be necessary. If severe hypoxemia is still present after the application of differential lung CPAP/PEEP, it should be remembered that the nondependent lung may be ventilated intermittently with positive pressure with oxygen. Finally, most of the ventilation-to-perfusion imbalance is eliminated during a pneumonectomy by tightening a ligature around the nonventilated lung pulmonary artery as early as possible, which directly eliminates all shunt flow through the nonventilated lung.

The second conclusion is that approximately one MAC halothane and isoflurane does not impair arterial oxygenation any more than does intravenous anesthesia during one-lung ventilation. This conclu-

sion is consistent with the notion that inhalation anesthetics have less of an inhibitory effect on HPV in intact animal preparations (13,83,92,99,106,110). Regardless of whether or not these inhalational anesthetics inhibit HPV, it is reasonable to recommend that since halothane and isoflurane have a number of desirable properties (permit the use of a high  $\text{FiO}_2$ , are rapidly eliminated, have a salutary effect on bronchomotor tone, and have few negative cardiovascular effects), and do not impair arterial oxygenation during human one-lung ventilation conditions, they are desirable anesthetics to use during one-lung ventilation and thoracic surgery.

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## Clinical Reports

### Aminophylline is an Antagonist of Lorazepam

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The ability of aminophylline to reverse flurazepam- and diazepam-induced sedation has been reported (1-3), but the effect of aminophylline on lorazepam, a relatively long-acting benzodiazepine, has not been described. The three case reports presented here suggest that aminophylline may be used to antagonize lorazepam.

#### Case 1

A 51-yr-old, 78-kg man was discovered to have a solitary nodule near the hilum of the right lung on routine chest x-ray. He was then scheduled for a bronchoscopy with brushings and biopsy under local anesthesia. The patient had a history of heavy cigarette smoking and chronic bronchitis but was receiving no medications. Preoperative serum electrolyte levels were normal. An arterial blood sample while breathing room air showed pH and  $PCO_2$  to be normal, but  $PO_2$  was 74 mm Hg. Pulmonary function studies demonstrated a moderate obstructive pattern. The ECG was unremarkable.

The patient was given 3 mg lorazepam orally 90 min prior to surgery, and 0.2 mg glycopyrrolate intravenously in the holding area 20 min prior to surgery. He was taken to the operating room very sedated yet able to respond to verbal commands. Five ml of 2% viscous lidocaine were given orally to anesthetize the oropharynx, and 3 ml of 4% lidocaine were injected transtracheally. Just prior to bronchoscopy, the larynx was directly visualized, and a small amount of 4% lidocaine was sprayed over the epiglottis and vocal cords.

The patient was given an additional 2 mg of lorazepam intravenously in divided doses during the

first 40 min of the procedure, at which time it was decided to convert to general anesthesia due to patient discomfort. At that time, 300 mg of thiopental were given, and 1% enflurane in oxygen was administered through a ventilating, rigid bronchoscope. The procedure lasted an additional 15 min, and the patient was stable but not responsive when taken to the recovery room. One hr later he responded to vigorous stimulation but was not oriented. An additional 45 min elapsed without change in his level of consciousness. One mg/kg of aminophylline was given intravenously over 10 min in an attempt to reverse the sedation of the lorazepam. Within 3 min the patient was alert, responsive, and oriented; and remained so without further intervention. He was discharged from the recovery room 90 min later, still alert.

#### Case 2

A 68-yr-old, 56-kg woman was scheduled for placement of a permanent pacemaker while under local anesthesia. Ten days earlier she had suffered a myocardial infarction complicated by bradyarrhythmias. She had a two-year history of stable angina treated by nitrates and propranolol. Preoperative laboratory values and a chest x-ray were normal, and the ECG showed a first-degree A-V block with evidence of an inferior myocardial infarction. The patient was given 10 mg of diazepam orally 60 min prior to surgery. She was very apprehensive during the procedure, and 2 mg of lorazepam were administered intravenously in divided doses during the 25-min procedure. This produced such profound sedation that she was transferred to the recovery room for observation. On admission to the recovery room her blood pressure and respiration were normal, but she remained difficult to rouse. There was no change in her level of consciousness after nearly an hour. At that time 1 mg/kg of aminophylline was given intravenously over a 5-10 min period in an attempt to reverse the lorazepam-

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induced sedation. She became very easy to rouse after this, although she remained mildly sedated. The patient was observed for an additional 60 min at which time she was discharged from the recovery room, awake and alert.

### Case 3

A 27-yr-old, 79-kg man was admitted for an arthroscopy of the right knee. Past history was negative except for the knee injury suffered while running. Chest x-ray, ECG, and laboratory values were normal. The patient elected to have the procedure done under epidural anesthesia. He was given 8 mg of morphine sulfate and 50 mg hydroxyzine intramuscularly 60 min before being brought to the regional block room, with minimal resultant sedation. An epidural catheter was easily placed at the L3-4 interspace, and anesthesia was obtained to the T10 level with incremental doses of 0.5% bupivacaine. The patient was then taken to the operating room where he was given 4 mg of lorazepam intravenously after being positioned on the operating table. Vital signs remained stable, and he continued to be very sedated during the 95 min procedure, after which he was transferred to the recovery room in stable condition, although responsive only to vigorous stimulation. The patient was still extremely somnolent two hr later, and reversal of the lorazepam was attempted by giving 2 mg of physostigmine over 5 min. This produced no change in his level of consciousness over the next 15 min. Reversal of the sedation was then attempted by giving 1 mg/kg of aminophylline intravenously over 10 min, and he showed marked improvement in his level of consciousness within 5 min. Twenty min later he again became drowsy, the same dose of aminophylline was repeated, and again he soon was alert and responsive. The patient was observed for an additional 60 min, during which time he remained alert, and was subsequently discharged from the recovery room.

### Discussion

Several authors report arousal after physostigmine administration after general anesthesia that included lorazepam or diazepam (4-6). The patients in these reports, however, received other drugs (including general anesthetics, phenothiazines, and atropine) that depress central cholinergic mechanisms. The reversal in these patients may have been due to antagonism of medications other than the benzodiazepines given during the anesthesia. Studies done where only benzodiazepines were used show failure of antagonism

with physostigmine (7,8). Naloxone also does not appear to reverse benzodiazepines (9).

Aminophylline has been used to reverse diazepam- and flurazepam-induced sedation (1-3). It has been used to improve ventilation in neonatal apnea (10), to reverse coma associated with cerebral vascular accidents (11), and to abolish Cheyne-Stokes respirations (12).

Although numerous studies have linked gamma-aminobutyric acid (GABA) to the mechanism of action of benzodiazepines (13,14), there appears to be purinergic involvement as well. Benzodiazepines appear to enhance extracellular adenosine levels in the CNS (15,16) possibly by blocking adenosine reuptake into neuronal and glial cells. Methylxanthines, such as theophylline, antagonize the depressant actions of adenosine and appear to reverse flurazepam- and diazepam-induced sedation (15,16). Xanthine derivatives without adenosine blocking properties are unable to reverse benzodiazepine-induced sedation (17). In summary, 1 mg/kg aminophylline rapidly reversed sedation associated with lorazepam in three patients.

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## Another Use for Mass Spectrometry: Detection and Monitoring of Malignant Hyperthermia

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Malignant hyperthermia (MH) is a hypermetabolic state with increases in both aerobic and anaerobic metabolism. This clinical report illustrates the early diagnosis of unsuspected malignant hyperthermia in a patient undergoing an emergency laparotomy in whom the usual clinical signs of MH were obscured by preexisting fever and tachycardia. Abnormally high end-tidal carbon dioxide values were measured by mass spectrometry, reflecting the increased metabolic rate.

### Case Report

A 24-kg, 8-yr-old boy presented for an emergency laparotomy for acute appendicitis. The patient had a clinical history of right lower quadrant pain of two days duration with fever (39°C), nausea, and vomiting. The past medical history was negative, and the patient had never received an anesthetic. The anesthetic history of the family, including parents, grandparents, and siblings was also negative.

Physical examination revealed a febrile child with tachycardia (150 beats/min), a tense abdomen, right lower quadrant guarding, and rebound tenderness. The white blood cell count was elevated with a left shift; serum electrolytes were within normal limits.

After preoxygenation, a rapid sequence induction of anesthesia was performed using thiopental, 4 mg/kg, and succinylcholine, 1.5 mg/kg. The trachea was intubated with a 6.0-mm cuffed oral tracheal tube. After induction, anesthesia was maintained with enflurane and 70% nitrous oxide. After return of sustained tetanus, muscle relaxation was obtained with curare, 0.4 mg/kg, as judged by twitch monitor. An esophageal temperature probe was placed, and the mass spectrometer sampling port was inserted into the anesthesia circuit at the proximal end of the endotracheal tube. The initial temperature reading was 39°C, which

agreed with the patient's preoperative temperature. As the abdominal incision was made, 5-7 min after induction, the end-tidal carbon dioxide was first noted to be abnormally elevated. The end-tidal CO<sub>2</sub> of 10% was recorded in spite of a minute ventilation of 7 L/min as measured by a Dräger Volumeter. Position of the endotracheal tube was checked, and breath sounds were bilaterally clear and equal. Concurrently, the abdomen was noted to be tense with protruding bowel, despite adequate relaxation as indicated by the twitch monitor. The temperature was again checked and noted to have risen to 40°C. The diagnosis of malignant hyperthermia was made.

The diagnosis of malignant hyperthermia was based on several facts: hypercapnia in the face of hyperventilation; increased muscle tension despite adequate muscle relaxation as judged by twitch monitor; and temperature elevation. Immediately and simultaneously, the minute ventilation was increased to 16 L/min, enflurane and nitrous oxide were discontinued, oxygen flow rate was increased, refrigerated intravenous solutions were started, and peritoneal lavage with cold saline was initiated. An arterial catheter was placed, and gastric lavage with cold saline was initiated together with packing the upper torso with ice. Surgery was not terminated because the patient was believed to have life-threatening peritonitis from a ruptured appendix.

The initial arterial blood sample, obtained 25 min after induction, had a pH of 7.15, PaO<sub>2</sub> of 120 mm Hg, PaCO<sub>2</sub> of 44 mm Hg, and base excess -12.8 mEq/L with an inspired oxygen concentration of 30%. Ionized calcium was 1.21 mM, potassium 4.8 mM, glucose 240 mg/dl. Mass spectrometry showed the end-tidal CO<sub>2</sub> was 7% at this time. The patient was given 45 mEq of bicarbonate and a total of 40 mg (1.7 mg/kg) of dantrolene intravenously in 20-mg increments, 5 min apart. Shortly after the second dose of dantrolene, the mass spectrometer indicated an abrupt decrease in end-tidal CO<sub>2</sub> to 2.5%. However, hyperventilation was maintained until a second arterial blood sample, taken 10 min after the second dantrolene dose, showed a pH of 7.74, PaCO<sub>2</sub> of 12 mm Hg, PaO<sub>2</sub> of

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586 mm Hg, and base excess  $-12.2$  mEq/L while 100% oxygen was being administered. Although the patient had severe acidemia, no further bicarbonate was given because of the very high arterial pH and concern for alkalotic rebound produced by lactate metabolism. The arterial  $\text{PCO}_2$  was raised to lower the pH. Mannitol was given to promote an osmotic diuresis, and the operation was completed as quickly as possible (20 min) using fentanyl and nitrous oxide.

Blood pressure remained stable, as did the heart rate, (initially 160–165 beats/min) during induction and intubation. Heart rate remained between 160–180 beats/min during most of the operation until suddenly increasing to 208 beats/min just prior to the dantrolene. The patient's temperature reached a maximum of  $41^\circ\text{C}$ .

The trachea was extubated in the operating room after reversal of muscle relaxation with neostigmine. Prior to extubation, the patient's temperature had decreased to  $38^\circ\text{C}$ , and arterial blood-gases were at a pH of 7.43,  $\text{PaCO}_2$  of 31 mm Hg,  $\text{PaO}_2$  of 277 mm Hg, base excess  $-1.7$  mEq/L with an  $\text{FiO}_2$  of 0.5. The patient was alert and oriented in the recovery room with normal arterial blood-gas tensions while breathing 6 L/min oxygen by face mask (pH of 7.42,  $\text{PaO}_2$  of 275 mm Hg,  $\text{PaCO}_2$  of 38 mm Hg, base excess  $+1.4$  mEq/L). A Foley catheter had been inserted while the patient was in the operating room, at which time the urine had appeared normal. In the recovery room the urine began to appear dark. The urine was dipstick positive for hemoglobin or myoglobin, or both, and quantitative urine myoglobin was ordered, but the result never returned to the chart.

The patient was transferred to an ICU and closely monitored for 24 hr. Urine output was enhanced by the administration of 1.5 times the volume of maintenance intravenous fluids. Serial serum CPK levels were 1350 in the recovery room and 11,600 12 hr postoperatively. The postoperative course was uneventful, with no further dantrolene being required and renal function remaining normal. The patient was discharged on the fifth postoperative day after intravenous antibiotic therapy for peritonitis.

## Discussion

The case described is of clinical importance because it demonstrates the value of routine monitoring of exhaled gases, including carbon dioxide. The potential value of expiratory carbon dioxide measurement in MH-susceptible patients has been recognized (1). This report substantiates its clinical value in the diagnosis and treatment of MH in humans.

Although the intracellular skeletal muscle defect of

MH is not well understood, the extracellular manifestations reflect the striking increase in both aerobic and anaerobic metabolism. The time course of physiologic events in malignant hyperthermia has been investigated using susceptible Landrace pigs after halothane anesthesia (2). The first major chemical change is the production of acidosis, accompanied by a simultaneous drop in blood pH and rise in blood  $\text{PCO}_2$ . The rise in temperature is secondary and follows the increase in blood  $\text{PCO}_2$  by 5 min. The metabolic acidosis during porcine MH is primarily due to lactic acid production, and individual case reports indicate that lactic acid is also the main factor in the metabolic acidosis of human MH (3,4). Thus a rise in blood  $\text{PCO}_2$  is one of the earliest signs of MH, and any unexplained rise in end-tidal  $\text{CO}_2$  concentration in the face of normally adequate minute ventilation should alert one to the possibility of malignant hyperthermia.

In the past, increased  $\text{CO}_2$  production has been noted by a rapid color change and increase in temperature of the carbon dioxide absorber (5). Increased carbon dioxide production in two patients with MH was measured postoperatively by Liebenschutz et al., and its decline was noted after dantrolene (6). Review of the literature has revealed only one case report whereby the initial diagnosis of MH was facilitated by direct real time measurement of end-tidal  $\text{CO}_2$  (7). Two cases of malignant hyperthermia were described in which the earliest sign was a rise in end-tidal  $\text{CO}_2$ . Elevation in temperature lagged behind hypercarbia even though both patients were initially normothermic. One patient exhibited no tachycardia.

In conclusion, a case of malignant hyperthermia was diagnosed by noting abnormally high end-tidal  $\text{CO}_2$  as measured by mass spectrometry. Preexisting tachycardia and hyperpyrexia obscured the usual clinical signs. Without capnography, the diagnosis and treatment of MH would have been delayed to the probable detriment of the patient. Early detection of MH, even in patients with normal vital signs, would be expected because elevation of blood  $\text{PCO}_2$  occurring simultaneously with the production of lactic acidosis occurs before temperature increase. In addition, management of MH was facilitated because an abrupt decrease in end-tidal  $\text{CO}_2$  signalled an endpoint to dantrolene administration.

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## Hydropneumothorax after Percutaneous Nephrolithotomy

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Percutaneous nephrolithotomy is a relatively new technique that is gaining popularity because, when successful, it saves a patient a large flank incision and long hospitalization. The procedure is intended to remove upper urinary tract stones through a nephrostomy tube placed previously under fluoroscopic control. A nephroscope is then inserted through the nephrostomy, the stones visualized, and removed in toto or by fragmentation. Removing the fragments requires large volumes of irrigation fluid (10–15 L) to flush the renal pelvis. The solution is usually isotonic saline, although glycine has also been used (1). The amount of fluid used for irrigation is directly related to the length of the procedure and the degree of difficulty in removal of the stone.

As with all new surgical techniques, the indications, contraindications, and complications are not completely defined. Complications reported in the literature include cardiac arrest (1), adult respiratory distress syndrome (2), extraperitoneal fluid extravasation (3), bleeding, and delayed rupture of a pseudoaneurysm (4). Two cases with other serious perioperative complications are described below.

### Case 1

The patient was a healthy 49-yr-old, 110-kg man with a 1.5 cm left renal stone at the ureteropelvic junction. Past history included a right pyelolithotomy for a calcium stone 3 yr before. Physical examination was unremarkable. Blood pressure was 130/80 mm Hg and pulse 76 beats/min. His hematocrit was 48%, serum sodium 141 mEq/L, and serum potassium 4.1 mEq/L. He was premedicated with morphine sulfate and glycopyrolate one hr prior to surgery.

Anesthesia was induced with thiopental and fentanyl with succinylcholine to facilitate tracheal intubation, after which anesthesia was maintained with

oxygen, nitrous oxide, isoflurane, fentanyl, and pancuronium. The monitors included an electrocardiogram, esophageal stethoscope, arterial blood pressure, blood gases, esophageal temperature, and ventilatory pressures. After cystoscopy, the patient was placed in the prone position and, after considerable difficulty, the stone was removed with the nephroscope from the left kidney. During the course of dilating the nephrostomy tract, some air bubbles were seen in fluid around the dilator, and the possibility of puncturing the pleura was mentioned by the surgeons. No changes in breathing sounds or ventilation pressure were noted at this time. However, toward the end of the 2-hr procedure, peak inspiratory pressures were noted to have increased from 20 cm during the earlier part of the case to 30 cm of water. About 12 L of normal saline had been used for irrigation during the procedure, but because of the prone position on blanket rolls and fluid on the floor, it was difficult to determine the input and output with accuracy. The pancuronium was reversed with neostigmine and glycopyrrolate at the conclusion of the procedure, but spontaneous respiration was labored. Upon putting the patient on his back on the recovery room cart, the absence of respiratory movement and breathing sounds on the left side of the chest and marked distention of the abdomen were obvious. The endotracheal tube was left in place, and the patient was transferred to the recovery room while respiration was assisted. An x-ray of the chest in the recovery room revealed a completely opacified left hemithorax with the mediastinum shifted to the right. The endotracheal tube was also visible on the x-ray in good position. The patient was semiconscious and cooperative. An arterial blood sample obtained while the patient was breathing 50% O<sub>2</sub> with manually assisted respiration showed a pH of 7.12, PCO<sub>2</sub> 64.7 torr, PO<sub>2</sub> 70 torr, and HCO<sub>3</sub><sup>-</sup> 20 mEq/L. A chest tube placed in the left hemithorax resulted in the prompt drainage of 1500 ml of light red fluid, and an abdominal tap produced 2600 ml of fluid over 45 min.

After drainage of the intrapleural fluid, the respiratory difficulty was much less, and after the peritoneal drainage was begun, the relief of abdominal

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distention made descent of the diaphragm possible so that spontaneous respiration approached normal. A repeat chest x-ray at this time showed no opacification of the left side of the chest and a small residual pneumothorax. Because of some facial edema, furosemide (5 mg) was given to help elimination of excess absorbed fluid.

The patient was distressed by the endotracheal tube and was extubated. A face mask with 100% O<sub>2</sub> was applied, and an arterial blood sample showed pH 7.23, PCO<sub>2</sub> 53 torr, PO<sub>2</sub> 97 torr, and HCO<sub>3</sub><sup>-</sup> 21.6 mEq/L. One hour later, still with 100% O<sub>2</sub> by mask, another blood sample showed pH 7.27, PCO<sub>2</sub> 49 torr, PO<sub>2</sub> 104 torr, and HCO<sub>3</sub><sup>-</sup> 21.8 mEq/L. Serum sodium was 143 mEq/L, potassium 3.7 mEq/L, and the hematocrit 44%. The patient received 14 mg of morphine sulfate during his 4-hr stay in the recovery room.

The patient was returned to the ward awake and oriented, with stable vital signs. The chest tube was left in place for one day. A nephrostogram the next day showed extravasated fluid in the posterior perirenal area with forward displacement of the kidney.

## Case 2

A 37-yr-old healthy man was scheduled for a right percutaneous nephrolithotomy for multiple stones. Past medical history and physical examination were unremarkable. Chest x-ray showed increased prominence of interstitial markings. Laboratory data included sodium 143 mEq/L, potassium 4.3 mEq/L, chloride 102 mEq/L, and hematocrit 49%. After thiopental for induction of anesthesia and succinylcholine for tracheal intubation, anesthesia was maintained with oxygen, nitrous oxide, isoflurane, and fentanyl. Monitoring in this patient included ECG, esophageal stethoscope, temperature, automatic blood pressure, and end-tidal carbon dioxide and ventilatory pressures. Two nephrostomy tracts were created, and two stones in the lower pole were destroyed with considerable difficulty using an ultrasonic probe. One stone in the upper pole could not be located. Fluid extravasation around the nephroscope was noticed by the surgeons. Peak inspiratory pressure needed to maintain adequate tidal volumes increased from 32 to 48 cm H<sub>2</sub>O in the fourth hour of surgery. An arterial blood sample after induction showed pH 7.38, PO<sub>2</sub> 95 torr, and HCO<sub>3</sub><sup>-</sup> 21.8 mEq/L. With the increase in peak inspiratory pressure, the arterial sample showed the pH to be 7.29, PO<sub>2</sub> 96 torr, PCO<sub>2</sub> 39 torr, and HCO<sub>3</sub><sup>-</sup> 21.9 mEq/L. Forty-eight liters of normal saline was used for irrigation with a measured return of approximately 25 L, with much lost on linen and on the floor. Extravasation of fluid in the right flank was

estimated at 8–10 L and blood loss was 1000 ml. End-tidal CO<sub>2</sub> remained stable (33–34 mm Hg) during the procedure. A perinephric drain was inserted and the procedure terminated after 4 hr and 45 min. An arterial blood sample in the recovery room, taken while the patient was breathing 50% O<sub>2</sub> spontaneously through an endotracheal tube, showed a pH of 7.29, PO<sub>2</sub> 81 torr, PCO<sub>2</sub> 36 torr, HCO<sub>3</sub><sup>-</sup> 18.5 mEq/L, and a base excess of -8.7 mEq/L. The patient was given 50 mEq of sodium bicarbonate. A chest x-ray taken while the patient was in the recovery room showed elevation of the right diaphragm and bilateral basilar atelectasis due to retroperitoneal fluid (rather than intraperitoneal fluid as in case 1). The patient was extubated after one hr with a tidal volume of 600–800 ml, vital capacity of 1600 ml, and a respiratory rate of 16. While the patient was breathing 50% O<sub>2</sub> with a face mask, arterial blood gas tensions were pH 7.32, PO<sub>2</sub> 101 torr, PCO<sub>2</sub> 45 torr, and HCO<sub>3</sub><sup>-</sup> 22.8 mEq/L. At the same time serum sodium was 145 mEq/L, potassium 3.9 mEq/L, and hematocrit 39%. The patient was transferred to the intensive care unit for overnight observation of his respiratory status. Respiratory therapy was started to prevent further atelectasis. The remaining stone was removed under general anesthesia six days after the first surgery without any complications. The patient's hematocrit dropped from 49% preoperatively to 39% immediately postoperatively, and to 34% on the fourth postoperative day. Serum potassium was 4.3 mEq/L preoperatively and decreased to 3.6 mEq/L on the second postoperative day.

## Discussion

The cause of hydropneumothorax in the first patient was a rupture of the pleura during the dilatation of the nephrostomy tract and gradual accumulation of irrigating fluid in the chest. Danger signs in this patient were air bubbles and increased peak inspiratory pressure, the cause of which was not immediately realized. Indeed, what had happened intraoperatively was not appreciated until the patient was placed in the supine position postoperatively and began breathing spontaneously. Intraanesthetic controlled ventilation opposed the effects of the hydrothorax, and the abdomen was not visible in the prone position.

In the second patient, fluid extravasation was noted around the nephroscope by the surgeon, but the first sign of respiratory problems was the increase in positive inspiratory ventilatory pressure. The fluid accumulated in the retroperitoneal area; thus, abdominal paracentesis would have been of little value.

In both patients stone removal was difficult and prolonged resulting in the use of large volumes of irrigation solution. Increased ventilatory pressures were the first signs of significant internal fluid extravasation. Both patients were in good general health and escaped serious morbidity, but similar complications in high-risk patients might well be life-threatening.

For early detection of significant extravasation, input and output of irrigating fluid and ventilatory pressures should be monitored closely. Any large discrepancy between input and output should alert the anesthesiologist to potential respiratory problems. Increasing ventilatory pressures were the earliest signs of extravasation in these cases. In the event of significant extravasation and increasing ventilatory pressures, consideration should be given to terminating the procedure. Monitoring of breathing sounds, end-tidal CO<sub>2</sub>, arterial blood gases, and pre- and post-operative body weight will also be helpful in detecting excessive fluid extravasation.

Intrarenal hemorrhage, which is difficult to control and estimate, can complicate this procedure. It is felt that the baseline hematocrit and electrolyte values would be valuable for identifying problems developing in the course of absorption of such large amounts of fluids, whether they be intraperitoneal or retroperitoneal, and for unidentified intrarenal blood loss.

It may be possible to increase the accuracy of fluid balance by using a watertight seal between the drapes and nephrostomy site and preventing fluid draining

underneath the drapes. This fluid can be collected in a bucket, a drape with a pocket, or suction bottle for closer measurement.

In summary, two cases of perioperative complications after percutaneous nephrolithotomy were discussed, together with their treatment and prevention. In our experience, rising ventilatory pressure, the amount of irrigation fluid used, and duration of surgery are the important indications for possible fluid extravasation. Percutaneous nephrolithotomy is becoming a common procedure but is clearly not without significant risk of complications.

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## Letters to the Editor

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### Closed Circuit Anesthesia is Accurate at any Altitude

To the Editor:

A recent article by James and White (1) reviewed the effects of altitude on the delivery of anesthetics and highlighted an inadequacy of the minimum alveolar concentration concept. Closed circuit anesthesia with potent volatile agents eliminates these difficulties. After closing the circuit, one thinks in terms of anesthetic absorption rather than the concentration of anesthetic to which the patient is exposed. When the body maintains a constant arterial concentration of a volatile anesthetic, a constant mass of agent (the unit dose) will be absorbed during each square-root-of-time interval (2). Because the density of a liquid such as halothane is independent of ambient pressure the unit dose of liquid injected into the circuit will be the same whether the anesthetist is at sea level, in a hyperbaric chamber, or on the top of Mt. Everest. This illustrates another advantage of the quantitative pharmacokinetics of the closed circuit over qualitative, concentration-oriented open systems.

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### Epidural Anesthesia in Patients with Spinal Fusion

To the Editor:

I read with interest Feldstein's and Ramanathan's (1) report on obstetrical anesthesia in patients with spinal fusion and would add my experience. Over the past five years, I have seen five similar obstetrical patients with only the L3-4 or the lower intervertebral spaces unfused. In four of them lumbar epidural anesthesia was easily induced. In the fifth patient, spinal anesthesia was used after blood was obtained on three attempts at the available L4-5 space.

Additionally, twelve obstetrical patients with Harrington rod spinal fusions extending from the T4 area through the L5-S1 intervertebral space insisted on receiving epidural anesthesia. The procedure and potential for failure were discussed thoroughly. In only one patient was the first attempt successful. In eleven patients, multiple attempts were necessary at various interspaces with both lateral and mid-line approaches using a 17-gauge Tuohy needle. Numerous "false spaces" were found in patients in whom ultimately no anesthesia developed. The epidural space was reached in six patients after fortuitously finding a defect in the fusion. In one of these six a dural puncture occurred. The needle was pulled back and a catheter inserted into what was believed to be the epidural space. Since no fluid was aspirated, 3 ml 0.25% bupivacaine were injected resulting in a T8 sensory level, suggesting spinal anesthesia. This patient required a cesarean section for cephalopelvic disproportion, and 5 ml 0.25% bupivacaine produced a profound motor block with a T4 sensory level. Recovery was uneventful without headache. In the remaining five patients with epidural anesthesia, three delivered vaginally and two required cesarean section for failure to progress. In all five patients, the volume and concentration of local anesthetic required to produce an adequate block were not different from patients without spinal fusion. The six patients in whom the epidural was successful had prepared childbirth with intravenous meperidine and local or pudendal block at the time of delivery. None of the twelve patients experienced complications or reported back pain postoperatively. All patients were pleased that epidural anesthesia had been attempted.

In summary, epidural anesthesia was attempted with Harrington rod spinal fusion in 17 patients and was accomplished in nine. Two of the 17 received spinal anesthesia. It is my opinion that an experienced epiduralist can safely attempt epidural anesthesia in the patient with spinal fusion for kyphoscoliosis.

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## An Unusual Complication of the Arrow Radial Artery Kit

To the Editor:

We have encountered an unusual complication using the Arrow Radial Artery Catheterization Set #R-04020 (a 20-gauge Teflon catheter advanced over a guidewire).

A 74-yr-old man was admitted for a total hip replacement. Because of a history of multiple pulmonary emboli and ventricular ectopy, radial artery catheterization was planned. After induction of general anesthesia, the 20-gauge thin-walled needle was inserted into the right radial artery, free return of blood was obtained, and the guidewire was advanced with ease. The catheter was then advanced without difficulty over the wire, using the Seldinger technique. Resistance was encountered when we attempted to remove the needle and wire; and, despite gentle manipulation of the wire and catheter, it was impossible to remove the wire. An arteriotomy was performed that revealed the wire entirely within the lumen of the artery. The distal end of the wire was, however, bent in such a way that it could not be pulled through the introducer. The bend probably came about when the tip of the wire impinged on the wall of the artery during insertion with the wire, becoming kinked before uncoiling as insertion continued. The entire assembly was removed, and a 20-gauge Quickcath was placed in the left radial artery. The operative and postoperative courses were otherwise uneventful.

We found we could repeat this complication with relative ease by putting a curve in this wire and then attempting to remove the wire through the catheter. This situation is similar to that which causes shearing of catheters when they are withdrawn through directional (e.g., Tuohy) needles.

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When faced with the problem of the coiling PAC, I have experienced frequent success with the following technique. After withdrawing the PAC to the SVC and inflating the balloon, I ask the patient to perform several deep breathing maneuvers while I advance the PAC until it just enters the RV. I then instruct the patient to perform a Valsalva maneuver (VM) as I observe on the monitor the traces of the electrocardiogram, the systemic arterial pressure, the central venous pressure (CVP), and the distal PAC pressure. A gradual increase in both CVP and PAC pressures confirms the patient's effective cooperation and is a signal to proceed with the PAC insertion. At this point the PAC usually follows the normal course and moves without coiling into the pulmonary artery. The patient is immediately told to breathe normally. I emphasize that the operator should proceed only after confirming an effective VM. Otherwise the danger of failure is common.

In my experience this technique is safe and helpful in this special circumstance. The VM is gentle and of brief duration. I have yet to notice any significant hemodynamic changes, either during or after the VM, other than in the right sided pressures, which are by themselves benign. By preventing the adverse consequences of repeated PAC coiling, namely arrhythmia generation and accidental knotting of the PAC, the safety of the procedure is enhanced. VM should not be considered a routine application, because PAC coiling is indeed uncommon.

It is tempting to speculate on a mechanism responsible for PAC coiling. I submit that dimensional changes or ejection fraction of the RV, or both, are important factors. I am not aware of any published work that sheds light on this supposition.

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## Valsalva Maneuver in Pulmonary Artery Catheterization

To the Editor:

Occasionally, pulmonary artery catheter (PAC) insertion is complicated by catheter coiling. When this occurs, the PAC first must be withdrawn, preferably to the superior vena cava (SVC), after which the insertion procedure may be repeated. Although unusual, the coiling sometimes recurs again and again. Repeated failures are frustrating, not only because of the time involved. The coil, which is most often in the right ventricle (RV), frequently causes potentially dangerous ventricular ectopic beats.

## Convulsions and Ventricular Tachycardia from Bupivacaine with Epinephrine: Successful Resuscitation— Congratulations!

To the Editor:

The treatment of bupivacaine-induced convulsions and ventricular tachycardia reported by Mallampati et al. (1) was successful because, as recommended by the ASA (2), prudent, vigilant anesthesiologists were prepared to treat the reaction promptly. Although it is difficult to fault success, we offer, nonetheless, the following comments.

Knowing that severe hypoxia, hypercarbia, and lactic acidosis occur concomitantly with local anesthetic-induced convulsions (3), succinylcholine, 80–100 mg intravenously—not diazepam or thiopental—with simultaneous ventilation by bag and mask using 100% oxygen is the immediate treatment of choice to stop convulsions rapidly (4–6). The advantages of succinylcholine are that it rapidly and consistently stops convulsions and thus lactic acid production; permits ventilation, which is the initial treatment of acidosis; allows tracheal intubation; does not depress the myocardium, as do thiopental, diazepam, and all local anesthetics; has a short half-life; and avoids fetal depression. Although hyperkalemia potentiates cardiotoxicity of local anesthetics (7,8), neither succinylcholine in absence of trauma (6,9), local anesthetics (6), nor lactic acidosis (6,10,11) produces hyperkalemia. Although succinylcholine has no effect on cortical electric seizure activity, such seizure activity has yet to be shown to be detrimental, provided the patient is rapidly and correctly treated (1,3,6,12–15).

Conversely, although diazepam and barbiturates dampen seizure activity, they do not consistently stop convulsions (1,16–18). Therefore, lactic acidosis production continues, ventilation is inadequate, and intubation may be impossible (1). Furthermore, both diazepam and barbiturates have negative inotropic effects on the myocardium, as do local anesthetics. Also, diazepam and barbiturates cause fetal depression and prolong postictal recovery.

The case report by Mallampati et al. suggests that bupivacaine, epinephrine, or both caused the ventricular tachycardia (1). What about the effect of intubation after the second seizure? Might not intubation in a nonventilated, hypoxic, hypercarbic, acidotic patient—not the local anesthetic solution—have triggered the ventricular tachycardia?

The dose of epinephrine used by Mallampati et al. to determine if the needle was in a vessel prior to injection of bupivacaine was 0.01 mg. Based on studies designed to evaluate components of a test dose (19), this dose provided only equivocal results of an intravascular injection in the case reported (1). Actually, 0.015 mg of epinephrine was required in their case, a dose routinely used to prevent intravascular injections during regional anesthesia for the past five years (19).

Finally, technical considerations are extremely important in all regional blocks. A syringe that holds no more than 10 ml should be used. Aspiration using a 30-ml plastic syringe (1) is not as reliable as aspiration using a 10-ml syringe, especially a glass one, because the former requires markedly greater force to overcome the friction of the plunger. This creates greater negative pressure, which can invaginate the wall of a blood vessel into the bevel of the needle, resulting in inability to withdraw blood. Perhaps more important, a 10-ml syringe acts as a safety factor when more than 10 ml is to be injected. Aspiration prior to, during, and after injection of its 10 ml at a rate of 1 ml/sec or slower (1 ml/2.4 sec in this case (1)), disconnecting the syringe from the needle, refilling, and reattaching it, as well as observing the electrocardioscope at appropriate intervals (prior to injection

and after each aspiration attempt), requires an elapsed time of approximately 30–40 sec (one circulation time). Therefore, if injected intravenously, 10 ml containing 1:200,000 epinephrine (0.05 mg) will produce a sustained tachycardia, which is recognizable on the electrocardioscope and should prevent injection of an additional 10 ml (19).

To conclude, this clinical report (1) and others (3,6,13–15) show that patients with bupivacaine-induced convulsions who are treated promptly can be resuscitated without sequelae. Also, although bupivacaine is cited for cardiotoxicity, one wonders about the severe lactic acidosis that accompanies convulsions (1,3,6,13,14) and can be life-threatening alone (10). Research in dogs (1), cats (16), and sheep (18) has indeed resulted in “pointing the finger” at bupivacaine as being cardiotoxic. Shouldn’t we also investigate the degree of lactic acidosis that may prevent successful resuscitation on its own, as well as defining more accurately what is meant by cardiotoxicity?

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## Use of Neurosurgical Patients for Muscle Relaxant Studies

To the Editor:

Matteo et al. recently reported on the differences in the pharmacokinetics and pharmacodynamics of *d*-tubocurarine and metocurine between old and young surgical patients (1). The two patient groups consisted of one group of 21 elderly (70-87 yr) patients for craniotomy that was compared with a group of 21 younger adults (21-59 yr) for craniotomy or carotid endarterectomy. The fact that the younger group included patients who were undergoing carotid endarterectomy introduces an unnecessary difference between the two patient groups. Hyperventilation, use of osmotic diuretics, antibiotics, and steroid administration are not a routine part of carotid surgery as they are in neurosurgical procedures. Also, Ornstein et al. have shown that phenytoin, a drug commonly used preoperatively in neurosurgical patients, was responsible for significantly decreasing the elimination half-life of metocurine (50% decrease from control) and increasing its plasma clearance (2). Ornstein et al. also showed that phenytoin made patients more resistant to the effects of metocurine, so that larger plasma concentrations of the drug were needed to reach various levels of neuromuscular blockade.

In order to interpret the data, readers must know whether or not the patients in the study by Matteo et al. were taking phenytoin. Also, I would submit that there are better surgical populations (i.e., cataract or orthopedic procedures) from which to choose patients to perform these important studies.

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### In Response:

As Dr. Fahey noted, there are differences between the surgical procedures performed on our younger and many of our elderly patients, but we do not believe the procedures in themselves affect drug action, distribution, or elimination.

Concerning the drugs administered, it has been shown that mannitol, the osmotic diuretic we employ, does not alter the kinetics of *d*-tubocurarine (1). The antibiotic used during surgery is oxacillin, a drug that does not interact with the nondepolarizing muscle relaxants. As a yet unpublished study has demonstrated, dexamethasone, a corticosteroid, given acutely as a bolus, does not alter a steady-state paralysis with pancuronium, metocurine, or *d*-tubocurarine. Further preliminary studies in patients chronically receiving dexamethasone also suggest there is no interaction with the nondepolarizers.

We are very much aware of the interaction of the nondepolarizers with phenytoin, and patients receiving the drug were excluded from this study. Incidentally, this interaction is apparent only when phenytoin is given chronically, and is not seen when phenytoin is given acutely to patients during a steady-state paralysis. There is a difference in arterial  $PCO_2$  between the two groups. We tend to maintain carotid endarterectomy patients' arterial  $CO_2$  in the low-to-mid 30s; while for craniotomies,  $CO_2$  is usually maintained in the mid 20s. The mean difference between the two groups is 4 torr. When only the elderly undergoing carotid endarterectomies were compared with the craniotomies, the mean difference was 6 torr. Katz et al. (2) reported that the neuromuscular blocking action of *d*Tc was reduced by hyperventilation. This effect was observed in 70% of the patients studied when the  $PCO_2$  had been lowered to a mean value of 18 torr. The mean differences in  $PCO_2$  between our two groups were relatively small and, in our opinion, unlikely to cause discernible differences in pharmacodynamic response between the young and elderly groups.

As to patient selection, certain groups of patients undergoing cataract or orthopedic procedures, especially those undergoing low-friction arthroplasty, contain a high percentage of elderly patients. In our institution, however, cataract surgery is too brief for our studies (30 min); and in those patients undergoing arthroplasty, hypotension is employed to reduce blood loss. Thus results from these latter patients cannot be interpreted with any degree of confidence. The attraction of neurosurgical patients for our studies is that cases are long, and there is usually minimal blood loss.

In summary, we believe that despite the problems, neurosurgical patients, including those undergoing craniotomy, can be used in studies of the pharmacokinetics and pharmacodynamics of muscle relaxants, provided care is exercised in their choice.

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## Equilibrium of 1% Halothane with Components of the Central Nervous System

To the Editor:

In a recent editorial (1) I said more than enough about the recent article by Johnson and Hartzell entitled "Choline Uptake, Acetylcholine Synthesis and Release, and Halothane Effects in Synaptosomes" (2). However, in their reply entitled "In Vivo MAC Values and In Vitro Experimentation" (3), the authors make so many statements contrary to chemical thermodynamics, I feel compelled to correct them before they become established in the anesthesia literature.

The authors prepared rat brain synaptosomes suspended in buffered saline solution and measured the effect of 3% gas phase halothane on a variety of enzyme activities. In my editorial I contended that the steep sigmoidal shape of the halothane dose-response curve meant that the results of their study were more relevant to cellular death than to anesthesia. In their reply to my editorial (3), they stated that "It is well established that halothane is one-third as soluble in buffered saline solution as in blood. Thus the concentration of halothane in saline at 3% gas phase halothane would approximate the same concentration of halothane in blood at 1% gas phase halothane." That statement is correct but is completely irrelevant with regard to the correct concentration of halothane in the gas phase over a synaptosome preparation. The reason that inhalation anesthesia works so well is that within a few minutes after induction of anesthesia, the entire body comes to chemical equilibrium with the concentration of inhalation anesthetic in the gas phase within the lungs. The thermodynamic driving force for a molecule of an inhalation anesthetic to leave the gas phase in the lung and enter the various fluids and tissues of the body is called its chemical potential. Gas molecules leave the gas phase in the lung, circulate with the blood, and diffuse into every muscle, intracellular space, fat layer, and nerve membrane until the chemical potential of halothane that corresponds to a 1% vapor phase exists in every tissue. When the chemical potential of halothane is equal in every compartment of the body, equilibrium is attained and no further concentration changes occur, although individual halothane molecules may be exchanged between various compartments.

Johnson and Hartzell are correct in stating that the concentration of halothane found in blood under these conditions will be about three times that found in a clear physiological fluid found in an intercellular space. However, the difference in these two concentrations has nothing to do with the concentration that the nerve tissue will reach. That concentration is defined solely by the 1% concentration of halothane in the gas phase in the lung.

As an illustration, consider a chamber containing a small beaker of buffered physiological saline and a small beaker of whole blood. If the chamber is flushed continually with 1% halothane in air, the solutions in the two beakers will soon reach the equilibrium concentration of halothane, roughly 1 mM in the physiological saline and 3 mM in the

whole blood. Now imagine that a small piece of the nerve membrane that the synaptosomes were made from is dropped into the beaker of physiological saline. It will rapidly absorb halothane molecules until the chemical potential of 1% halothane in the gas phase equals the chemical potential in the physiological saline (roughly 1 mM concentration), which also equals the chemical potential in the fragment of nerve membrane (roughly 20 mM concentration). The crucial error of Johnson and Hartzell is they did not realize that if a similar membrane fragment were dropped into the beaker of whole blood (with a concentration of roughly 3 mM halothane), the fragment of tissue will absorb anesthetic molecules until it reaches the identical 20 mM concentration of halothane that it did in the saline, not the 60 mM they predict. The reason for this goes back to the concept of chemical potential. Although there is a three-fold higher concentration of halothane in whole blood, the blood has a corresponding three-fold greater affinity for halothane molecules, and the halothane molecules do not leave the blood as readily for diffusion into the nerve membrane fragment. If one simply laid a similar piece of this nerve membrane fragment on the floor of the chamber containing 1% halothane, it would soon reach equilibrium and contain the same concentration of 20 mM halothane. Of course it would soon dry out, which is why physiological buffers are used for nerve membrane preparations, not because they have any effect on the halothane concentration in a nerve equilibrated with 1% gas halothane.

If one were to measure the concentration of halothane in the same nerve membrane fragment when it is contained within the brain of a patient at equilibrium with 1% halothane, it would measure 20 mM! That is why the additional concerns expressed by Johnson and Hartzell in their reply to my editorial (3), that the concentration of anesthetic may vary whether the cell is closed, or broken and disrupted, are totally without basis. If they maintain their gas phase in equilibrium with 1% halothane, then the halothane concentration in any particular membrane fragment will be constant whether the cell is intact, disrupted, or dissolved in saline, whole blood, or olive oil.

In summary, I must repeat my original criticism. A concentration of 3% halothane triples the chemical potential of halothane and causes a corresponding tripling of every concentration in every compartment in the body. However, the steep dose-response curve of inhalation anesthetics means that those three-fold higher concentrations will be able to affect neurophysiological functions that have no relevance to the state of clinical anesthesia.

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## Book Reviews

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### Clinical Transcutaneous Electric Nerve Stimulation

Jeffrey S. Mannheimer and Gerald N. Lampe.

Philadelphia: F.A. Davis Company, 1984, 636 pp, \$42.00.

The foreword to this book claims, "This text presents in one volume a concise, yet complete discussion of pain, both as a symptom and pathology, and methods that may be employed for its management." Unfortunately the book is neither complete nor concise, though it would have been had the editors organized the book so that all the general and specific information concerning pain came prior to the transcutaneous nerve stimulation material. The editors intended the volume "to support and enhance the utilization of transcutaneous electrical nerve stimulation (TNS), [and to] define its role in the treatment of acute, chronic, and postoperative pain." It was not intended as a comprehensive guide to pain treatment, although some of the contributors do provide superficial, distracting information on non-TNS pain treatment.

The text does present a good review of pain, including chapters on psychologic considerations, afferent input and theory of pain modulation, pain as an indicator of pathology, and the nature and delineation of pain via its characteristics. There is excellent material concerning every conceivable aspect of transcutaneous nerve stimulation, including an informative, but all too brief historical review of the medical uses of electricity by Dr. Allan Hymes.

Overall, the book is a valuable reference for physical therapists and other health professionals who use TNS in pain treatment. The excellent illustrations, figures, and tables, along with the detailed bibliography add immensely to its value.

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### The Kidney in Anesthesia

Hans-Joachim Priebe. Boston: Little Brown & Co., 1984, 226 pp, \$24.00.

The editor begins his preface, "Anesthesiologists have developed in their work an intimate relationship with the heart and the lungs. By contrast, many anesthesiologists still believe that we stand on uncertain ground with the kidneys." Should these anesthesiologists read this volume in the International Anesthesiology Clinics series, they would gain a firmer foothold.

Of the 226 pages, about two-thirds cover basic topics, beginning with renal physiology and circulation and progressing through evaluation of renal function, renal failure, and diuretics. The last third is clinical and examines effects of anesthesia on renal function, anesthetic considerations for patients with renal disease and for those undergoing transplantation, and ends with respiratory support and renal function.

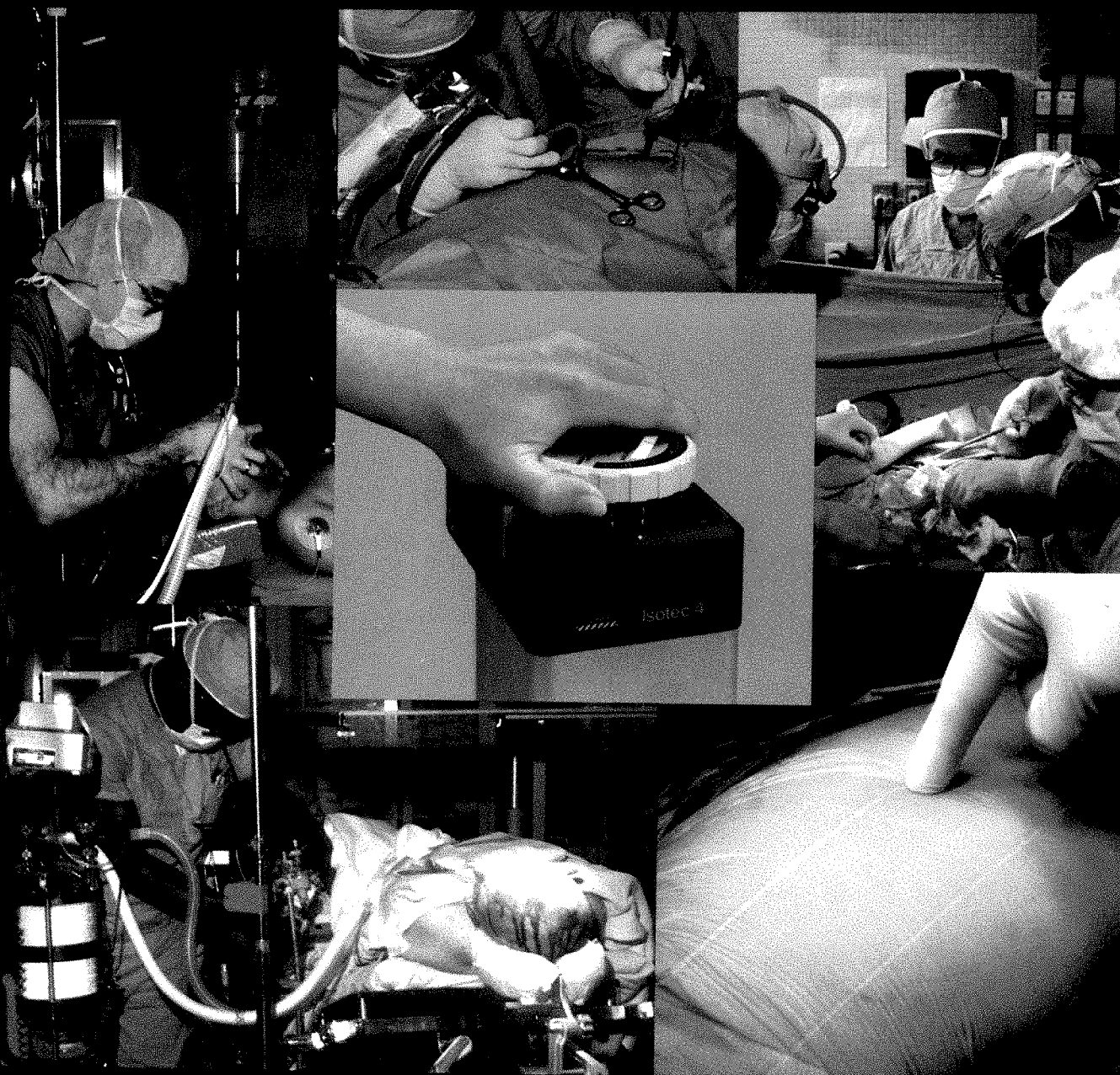
The chapters are well-written, direct, and to-the-point; all pertinent topics are covered. However, in a book this size, coverage is not always in great depth and statements are made that might gloss over controversy, e.g., is 5 min of preoxygenation really needed before rapid-sequence induction. Atracurium is barely discussed; the volume was issued in the spring of 1984. References for many of the chapters are old. Those in the last four clinical chapters have a median age over ten years. Perhaps the subject, though important, is static in terms of important recent advances.

Though part of a series, some issues have been released separately. This one may be worth purchasing by the reader who wants a broader review of the kidney and anesthesia.

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# **Forane<sup>®</sup> (isoflurane)**

## **The Versatile Anesthetic**



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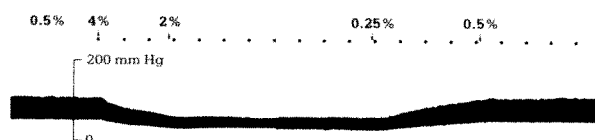
**Forane<sup>®</sup> (isoflurane)**



# Forane<sup>®</sup> (isoflurane) The Versatile Anesthetic

## A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.<sup>1</sup>



Blood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.<sup>1</sup>

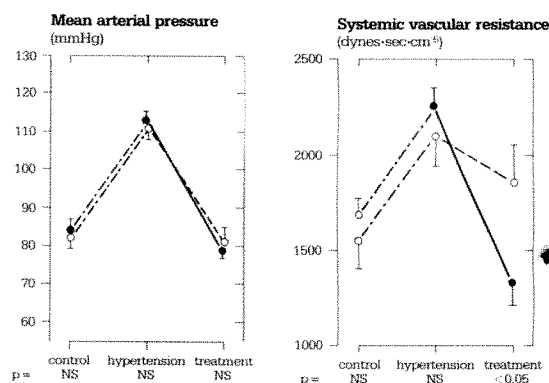
## Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when  $\text{PaCO}_2$  is controlled at 25-30 torr, and ICP may be readily lowered during surgery by decreasing  $\text{PaCO}_2$ .<sup>2</sup>

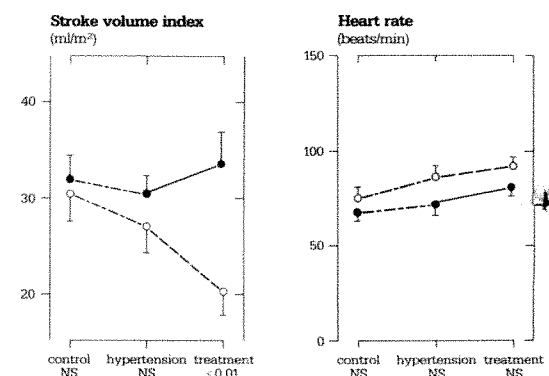
## Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery (Adapted from Hess et al<sup>3</sup>).



● — Pretreatment (fentanyl, flunitrazepam, pancuronium)  
● — Treatment with isoflurane  
○ — Treatment with halothane





## Potential of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).<sup>4,5</sup> Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

## Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."<sup>6</sup>

## A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."<sup>7</sup> (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.<sup>8</sup>

Post-laparoscopy Nausea (N) and Vomiting (V)		
Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N <sub>2</sub> O, O <sub>2</sub>	37	23 (62%)*
isoflurane, fentanyl, O <sub>2</sub>	20	6 (30%)
isoflurane, O <sub>2</sub>	20	5 (25%)

Adapted from Alexander et al<sup>8</sup> \*p<0.05

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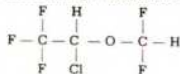
**Forane® ...a product of original Anaquest research**  
(isoflurane)



# Forane®...The Versatile Anesthetic (isoflurane)

**CAUTION:** Federal Law Prohibits Dispensing without Prescription

**DESCRIPTION:** FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Some physical constants are:

Molecular weight	184.5
Boiling point 760 mm Hg	48.5°C (Uncorr.)
Refractive index $n_D^{20}$	1.2990—1.3005
Specific gravity 25°/25°C	1.496
Vapor pressure in mm Hg **	
20°C	238
25°C	295
30°C	367
35°C	450

\*\* Equation for vapor pressure calculation:

$$\log_{10} P_{\text{vap}} = A + \frac{B}{T} \quad \text{where: } A = 8.056$$

$$B = -1664.58$$

$$T = ^\circ\text{C} + 273.16 \text{ (Kelvin)}$$

Partition coefficients @ 37°C	
Water/gas	0.61
Blood/gas/gas	1.43
Oil/gas	90.8
Partition coefficients @ 25°C—rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinylchloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec and 23°C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec and 23°C	Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave UV light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali; indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

**CLINICAL PHARMACOLOGY:** FORANE (isoflurane) is an inhalation anesthetic. The M.A.C. (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N <sub>2</sub> O
25 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation of tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO<sub>2</sub>, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 ml of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

**Pharmacokinetics:** Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

**INDICATIONS AND USAGE:** FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

**CONTRAINDICATIONS:** Known sensitivity to FORANE (isoflurane) or other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

**WARNINGS:** Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients

undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

**PRECAUTIONS: General:** As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

**Information to Patients:** Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

**Laboratory Tests:** Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

**Drug Interactions:** Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and M.A.C. (minimum alveolar concentration) is reduced by concomitant administration of N<sub>2</sub>O. See Clinical Pharmacology.

**Carcinogenesis:** Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/6, and 1/32 M.A.C. for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

**Pregnancy Category C:** Isoflurane has been shown to have possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

**Malignant Hyperthermia:** In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO<sub>2</sub> absorption system (hot canister). PaO<sub>2</sub> and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

**ADVERSE REACTIONS:** Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting, and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

**OVERDOSAGE:** In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

**DOSEAGE AND ADMINISTRATION: Premedication:** Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

**Inspired Concentration:** The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

- vaporizers calibrated specifically for isoflurane;
- vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula

$$\% \text{ isoflurane} = \frac{100 P_A P_V}{F_T (P_A - P_V)}$$

where  $P_A$  = Pressure of atmosphere  
 $P_V$  = Vapor pressure of isoflurane  
 $F_T$  = Flow of gas through vaporizer (ml)  
 $F_T$  = Total gas flow (ml)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

**Induction:** Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

**Maintenance:** Surgical levels of anesthesia may be sustained with a 1.0-2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5% to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

**HOW SUPPLIED:** FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 ml amber-colored bottles.

**Storage:** Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

Revised 1-83

## Anaquest Forane® (isoflurane)

Anaquest  
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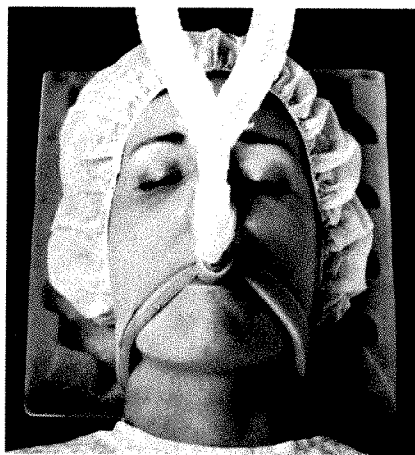
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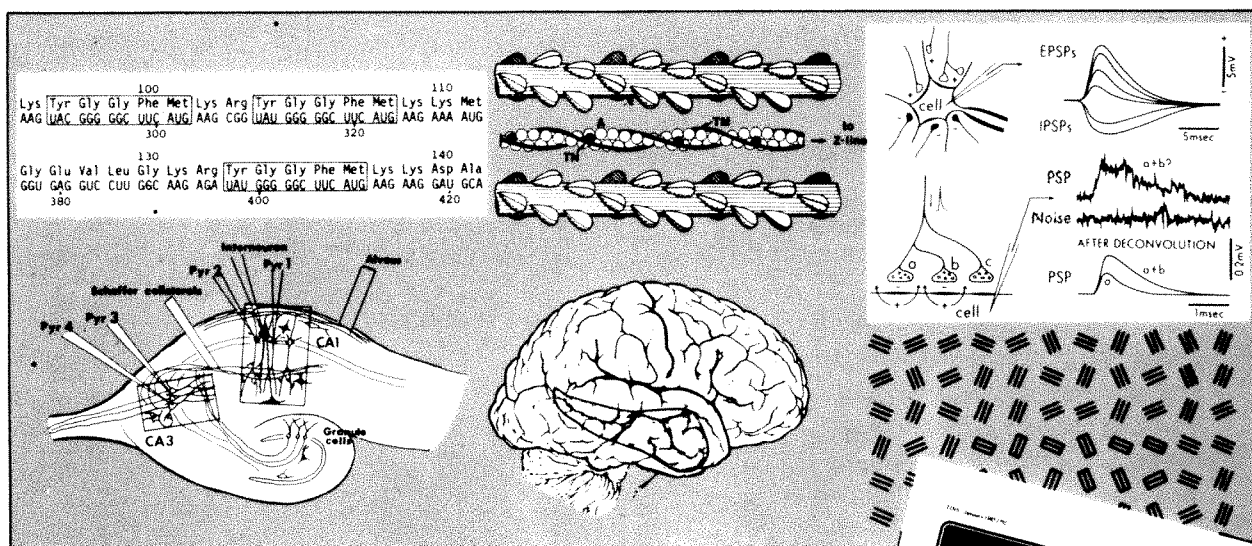
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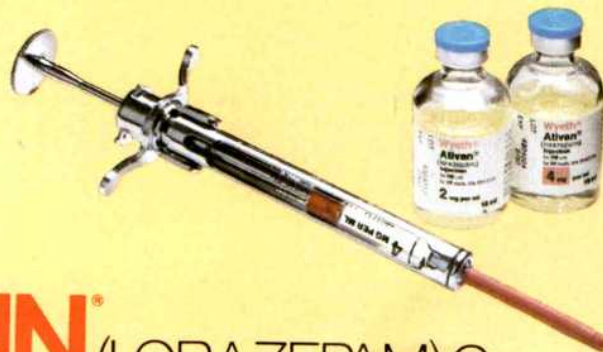
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The dosage of Ativan® (lorazepam) Injection should be individualized for each patient. For those in whom reduced recall and excellent sedation are desired, doses of 0.05 mg/kg up to a maximum of 4 mg should be administered. For patients in whom lack of recall is not desired, and for the elderly or debilitated, the dose should be reduced.



**ATIVAN®** (LORAZEPAM) <sup>IV</sup>  
**INJECTION** IM or IV

**Wyeth Laboratories**  
Philadelphia, PA 19101

See important information on following page.



# ATIVAN® (LORAZEPAM) INJECTION IM or IV

**DESCRIPTION:** Ativan® (lorazepam) injection, a benzodiazepine with anxiolytic and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-( $\alpha$ -chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

**CLINICAL PHARMACOLOGY:** IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

**INDICATIONS AND USAGE:** In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

**CONTRAINDICATIONS:** Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See WARNINGS)

**WARNINGS:** PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION. THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal failure. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam. Their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

**Pregnancy:** LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chloridiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

**Endoscopic Procedures:** There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

**PRECAUTIONS: General:** Bear in mind additional CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE AND ADMINISTRATION.) When lorazepam is used IV as premedication prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

**Information for Patients:** As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedication that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effects, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

**Laboratory Tests:** In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

**Drug Interactions:** Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

**Drug/Laboratory Test Interactions:** No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

**Pregnancy:** Pregnancy Category D. See WARNINGS section.

**Labor and Delivery:** There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

**Nursing Mothers:** Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

**Pediatric Use:** There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

**ADVERSE REACTIONS: CNS:** Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/448) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE AND ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedication). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

**Local Effects:** IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately post-injection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

**Cardiovascular System:** Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

**Respiratory System:** Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

**Other Adverse Experiences:** Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

**DRUG ABUSE AND DEPENDENCE:** As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

**OVERDOSSAGE:** Overdose of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdose is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

**DOSAGE AND ADMINISTRATION:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

**Intramuscular Injection:** For designated indications as premedication, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedications, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure. Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

**Intravenous Injection:** For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to a total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure. EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

**Administration:** When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP; Sodium Chloride Injection, USP; 5% Dextrose Injection, USP.

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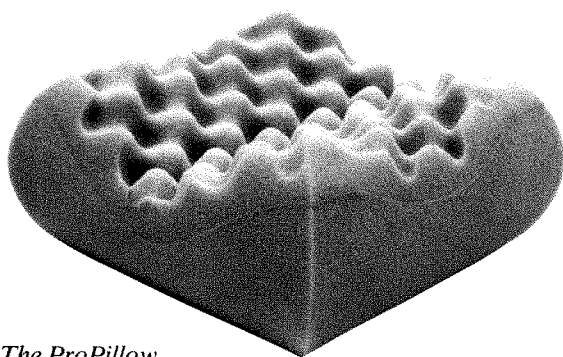
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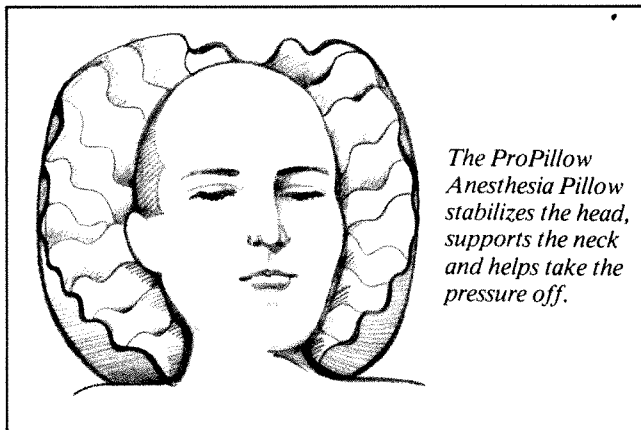
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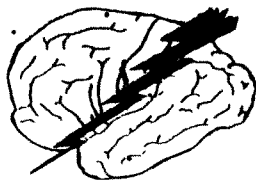
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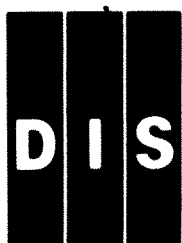
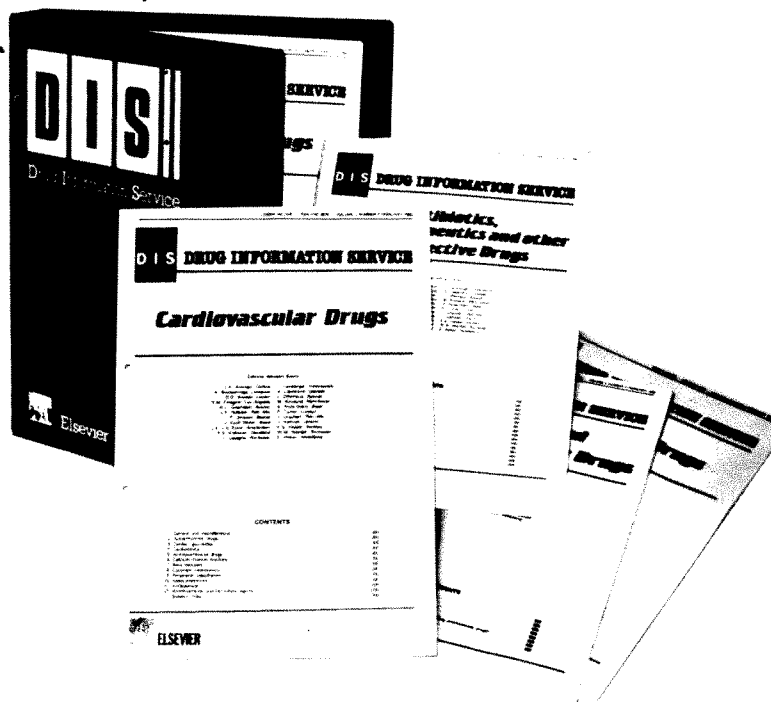
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# 1974:

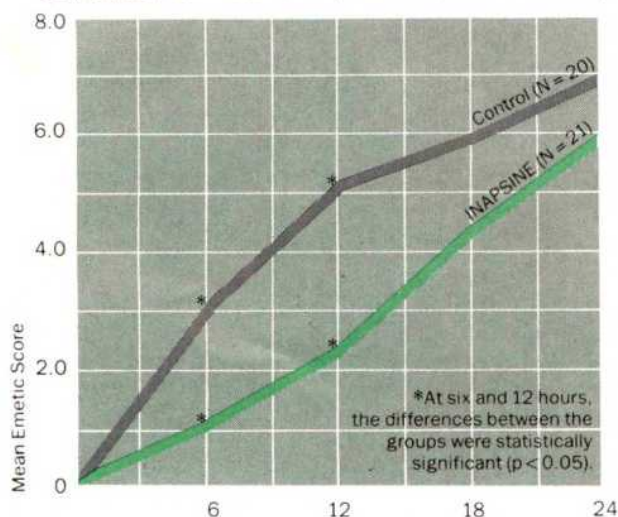
“...we found droperidol [INAPSINE®] to be a safe and effective prophylactic anti-emetic agent in this group of patients at high emetic risk.”<sup>①</sup>

# 1984:

“The incidence of postoperative nausea/vomiting... was higher in patients who received hydroxyzine as premedicant compared to those who received droperidol [INAPSINE] ( $p < 0.05$ ).”<sup>②</sup>

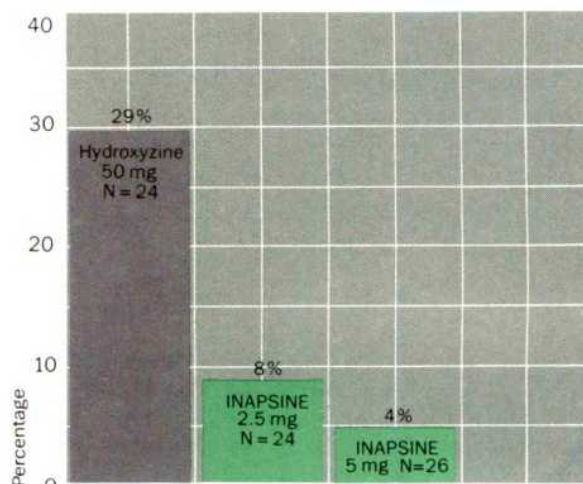
Double-blind study of 41 patients undergoing hysterectomy. Twenty-one patients received 5 mg INAPSINE shortly after surgery began, while 20 patients received placebo. Postoperative emesis was rated according to an emetic scoring system. Patients receiving INAPSINE had significantly less frequent and less severe nausea, retching and vomiting during the first 12 postoperative hours.

INAPSINE vs placebo: mean total emetic scores. The lower the score, the fewer and less severe the incidents of emesis. (Adapted from Patton CM Jr, Moon MR, Dannemiller FJ<sup>1</sup>)



Double-blind comparison of INAPSINE 5 mg, INAPSINE 2.5 mg and hydroxyzine 50 mg, combined with meperidine or morphine and glycopyrrolate, as premedication in 74 women undergoing major elective gynecologic surgery. Significantly fewer of the patients receiving INAPSINE experienced postoperative nausea/vomiting than those receiving hydroxyzine ( $p < 0.05$ ).

Percentage of patients experiencing postoperative nausea/vomiting according to premedication ( $p < 0.05$ ). (Based on Mehta P, Theriot E, Mehrotra D, et al<sup>2</sup>)



Before prescribing please consult complete prescribing information, of which the following is a brief summary. Protect from light. Store at room temperature. FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY. Droperidol is a neuroleptic (tranquilizer) agent.

**DESCRIPTION:** 2 ml and 5 ml ampoules. Each ml contains Droperidol 2.5 mg and lactic acid for pH adjustment to  $3.4 \pm 0.4$  10 ml vials. Each ml contains Droperidol 2.5 mg with 1.8 mg methylparaben and 0.2 mg propylparaben, and lactic acid for pH adjustment to  $3.4 \pm 0.4$ .

**INDICATIONS:** INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; • in neurolept analgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

**CONTRAINDICATIONS:** INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

**WARNINGS:** FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should

be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as  $1/4$  to  $1/2$  those usually recommended.

**PRECAUTIONS:** The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy.

Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be



# Documenting a Decade of Significantly Superior Antiemetic Protection

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The Premedication That Does More Than Premedicate

### References:

- 1 Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Analg* 1974;53:361-364.
- 2 Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Cur Ther Res* 1984;35:715-720.

found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

**ADVERSE REACTION:** The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and post-operative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur, if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

**DOSAGE AND ADMINISTRATION:** Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

### Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg (1 to 4 ml) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia

Induction—2.5 mg (1 ml) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.

Maintenance—1.25 to 2.5 mg (0.5 to 1 ml) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

If INNOVAR<sup>®</sup> injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg (1 to 4 ml) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg (0.5 to 1 ml) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg (1 to 2 ml) may be administered intramuscularly or slowly intravenously when additional sedation is required.

**How Supplied:** 2 ml and 5 ml ampoules—packages of 10.

10 ml multiple-dose vials—packages of 10.

U.S. Patent No. 3,161,645

NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10

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